Empathie und deren neuronale Korrelate bei Patienten mit Borderline-Persönlichkeitsstörung

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vorgelegt von
Dipl.-Psych. Sandra Preißler

Präsident der Humboldt-Universität zu Berlin
Prof. Dr. Jan-Hendrik Olbertz

Dekan der Mathematisch-Naturwissenschaftlichen Fakultät II
Prof. Dr. Elmar Kulke

Gutachter: 1. Prof. Dr. Thomas Fydrich, Humboldt-Universität zu Berlin
2. Prof. Dr. Michael Niedeggen, Freie Universität Berlin
3. PD Dr. Thomas Straube, Friedrich-Schiller-Universität Jena

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1. Einleitung

Das Verstehen und Verarbeiten emotionaler Erfahrungen anderer Menschen, im Sinne allgemeiner sozialer und empathischer Fähigkeiten, gehört zur normalen psychischen Entwicklung und Sozialisation. Es trägt wesentlich zu einer gesunden zwischenmenschlichen Beziehungsgestaltung bei. Bei Menschen mit Borderline-Persönlichkeitsstörung (BPS) ist genau diese Fähigkeit zur Beziehungsgestaltung aufgrund von Problemen in der interpersonellen Kommunikation auffällig beeinträchtigt. Eine mögliche Ursache dafür könnten veränderte empathische Fähigkeiten bei Patienten mit BPS sein. Empathie wird als ein multidimensionales Konstrukt verstanden, das aus kognitiven (dem Verstehen mentaler Zustände, „Theory of Mind“ (ToM)) und affektiven Anteilen (der emotionalen Reaktion auf den Gemütszustand eines anderen) besteht.

Mit dieser kumulativen Dissertation werden drei Publikationen und zwei Manuskripte eingereicht, die unterschiedliche Facetten dieser Problematik betrachten. Zuerst werden drei Studien vorgestellt, die die empathischen Fähigkeiten von BPS Patienten mit ökologisch validen Testverfahren auf der Verhaltensebene näher untersuchen. Die gefunden Defizite bei BPS werden dargelegt und der Einfluss von zwei häufig komorbid auftretenden Störungen, Posttraumatische Belastungsstörung (PTBS) und Narzisstische Persönlichkeitsstörung, wird überprüft.

Um zu demonstrieren, dass bestimmte funktionale und anatomische störungsspezifische Veränderungen die gefundenen veränderten empathischen Fähigkeiten bedingen können, werden anschließend neuronale Korrelate für kognitive und emotionale Empathie sowie bisher gefundene Abweichungen in Anatomie und Funktion des Gehirns bei Patienten mit BPS skizziert. Dazu erfolgt die Darlegung zwei weiterer empirischer Untersuchungen, die erstmalig die neuronalen Korrelate der spezifischen empathischen Defizite bei Patienten mit BPS untersuchen und den Einfluss einer komorbiden PTBS betrachten. Zusätzlich erfolgt die Beschreibung anatomischer Veränderungen bei Patienten mit BPS unabhängig von einer komorbid auftretenden PTBS. Abschließend werden die empathischen Fähigkeiten von Patienten mit BPS zusammenfassend diskutiert.

2. Borderline-Persönlichkeitsstörung

Personen mit Borderline-Persönlichkeitsstörung (BPS) sind nach DSM IV-TR (American Psychiatric Association, 2000) durch ein tiefgreifendes Muster von Instabilität in zwischenmenschlichen Beziehungen, im Selbstbild und in den Affekten sowie durch deutlich hohe Impulsivität charakterisiert. Einstellungen und Gefühle anderen Menschen gegenüber können stark und ohne erkennbare Ursache schwanken. Die Emotionen von Menschen mit BPS ändern sich schnell von leidenschaftlicher Idealisierung bis hin zu verächtlicher Wut oder Verachtung. Personen mit BPS sind leicht kränkbar, streitsüchtig, reizbar und sarkastisch. Ihre Impulsivität und Unberechenbarkeit sind potenziell selbstschädigend. Dazu zählen u.a. unüberlegte Geldausgaben, pathologisches Essverhalten und risikoreiche Sexualität. Hinzukommen bei Personen mit BPS selbstverletzende Verhaltensweisen und chronische Suizidalität. Für das nähere Umfeld ist es insgesamt schwer, mit Personen mit BPS zu leben (Davidson & Neal, 2002).

BPS kommt bei bis zu 5,9% der Allgemeinbevölkerung vor (Grant et al., 2008). Innerhalb der Diagnosekriterien des DSM IV-TR konnten drei Symptomkategorien identifiziert werden: affektive Dysregulation, Impulsivität (behaviorale Dysregulation) und Muster „gestörter Beziehungen“ (Sanislow et al., 2002). Affektive Dysregluation und Impulsivität wurden bereits in vielen empirischen Arbeiten betrachtet. Diese beiden Symptomkategorien konnten u.a. in Langzeitstudien (Zanarini, Frankenburg, Hennen, Reich & Silk, 2005), auf Verhaltensebene (Domes, Schulze & Herpertz, 2009), und in fMRT Studien (Domes et al., 2009) als mögliche Phänotypen von BPS identifiziert werden.

Im Gegensatz dazu wurde die Kategorie “gestörte Beziehungen” bisher nur in wenigen Studien untersucht (z.B. Hill et al., 2008; King-Casas et al., 2008; Skodol et al., 2005). Trotz des Mangels an Untersuchungen zeigte sich, dass das Beziehungsverhalten von Patienten mit BPS einer der besten Diskriminatoren für diese Persönlichkeitsdiagnose zu sein scheint (Gunderson, 2007). Eine mögliche Ursache für gestörtes Beziehungsverhalten im Allgemeinen könnte in der Störung der empathischen Fähigkeiten liegen (Davis & Oathout, 1987).

3. Empathie

3.1 Definition von Empathie

Empathie erleichtert soziale Interaktion. Sie erlaubt, die Reaktionen eines anderen zu verstehen und angemessen darauf reagieren zu können. Der Begriff „Empathie“ wird in der Wissenschaft vielseitig verwendet (Blair, 2005b; Davis, 1983; Leiberg & Anders, 2006; Singer, 2006). Empathie bezieht sich u.a. auf die Fähigkeit mentale und emotionale Zustände anderer zu erkennen (Decety & Meyer, 2008; Singer, 2006). Das kann sich sowohl auf der kognitiven Ebene, durch Verstehen der Emotion (kognitive Empathie), oder auf der emotionalen Ebene, durch sich in die Person Einfühlen (emotionale Empathie), vollziehen.

Kognitive Empathie entspricht dem Erkennen von Emotionen, Absichten und Gedanken anderer (Baron-Cohen & Wheelwright, 2004). Synonym werden für dieses Konzept die Begriffe „Theory of Mind“ (ToM; Premack, Woodruff & Kennel, 1978), soziale Kognition oder „mentalizing“ (Blair, 2005b; Frith & Frith, 2006) gebraucht.

Neben dem Verstehen der Absichten, Gedanken und Emotionen anderer Menschen besteht Empathie aber auch aus der Komponente des „sich Einfühlens“ in den Anderen. Es ist die emotionale Reaktion auf eine Emotion, die bei einer anderen Person beobachtet worden ist (Blair, 2005b; Davis, 1994; Eisenberg & Miller, 1987; Mehrabian & Epstein, 1972; Rogers, 1959). Emotionale Empathie ist demnach die emotionale Reaktion auf die emotionalen Signale anderer (Gesichtsausdruck, Stimmlage, Tonfall und Körperhaltung).

3.2 Erfassung von Empathie

Es gibt verschiedene Testverfahren zur Erfassung von Empathie. Für eine Übersicht über Fragebogenverfahren zur Erfassung von unterschiedlichen Facetten von Empathie wird auf die Arbeiten von Leibetseder (Leibetseder, Laireiter, Riepler & Köller, 2001) und Cliffordson (2001) verwiesen. In den hier vorgestellten Studien werden zwei „klassische“ Messverfahren für Empathie, der „Reading the Mind in the Eyes“-Test (RME; Baron-Cohen, Wheelwright, Hill, Raste & Plumb, 2001), und der „Interpersonal Reactivity Index“ (IRI; Davis, 1983) sowie zwei neu entwickelte Verfahren, der „Movie for the Assessment of Social Cognition” (MASC; Dziobek et al., 2006) und der „Multifaceted Empathy Test” (MET; Dziobek et al., 2008) eingesetzt. Der MET und der MASC zeichnen sich besonders durch ihre ökologische Validität aus. Alle vier Testverfahren sollen im Folgenden kurz näher beschrieben werden.

3.2.1 Der Reading the Mind in the Eyes Test

Als „klassisches" Messinstrument für kognitive Empathie gilt der "Reading the Mind in the Eyes Test" (RME; Baron-Cohen et al., 2001). Seine Aufgabe ist es, den mentalen Zustand der dargestellten Person anhand ihrer Augenregion zu identifizieren und die richtige Antwort aus vier Alternativen zu wählen. Der Test besteht aus 40 Items und wird bewertet indem die Summe der richtig genannten Items gebildet wird. Allerdings ist für dieses Testverfahren anzumerken, dass Daten zur Reliabilität rar sind. In einer schwedischen Studie wurde von einer mäßigen Re-Test-Reliabilität berichtet (Hallerback, Lugnegard, Hjarthag & Gillberg, 2009). In **Publikation A** (Preißler, Dziobek, Ritter, Heekeren & Roepke, 2010) wurde dieses klassische Testverfahren dennoch verwendet, da es bei Patienten mit BPS bereits zur Anwendung kam (z. B. Fertuck et al., 2009). In **Publikation A** hatte der RME eine akzeptable interne Konsistenz (Cronbach's Alpha (α) = 0, 71). Der Fokus dieser Studie lag allerdings auf dem im Folgenden erläuterten Messverfahren für kognitive Empathie, dem MASC (Dziobek et al., 2006).

3.2.2 Der Movie for the Assessment of Social Cognition

Der MASC (Dziobek et al., 2006; Fleck et al., 2006) ist ein ca. 45-minütiges, computergestütztes, ökologisch valides Testverfahren zur Erfassung sozialer Kognition. Er besteht aus einem 15-minütigen Film, der an verschiedenen Stellen stoppt. Dort werden eine Frage in der Form: „Was denkt/fühlt/beabsichtigt Person NN?" und vier Antwortmöglichkeiten eingeblendet (siehe Abbildung 1). Die Antwortalternativen unterteilen sich in sozial kognitiv treffend interpretiert, sozial überinterpretiert, sozial zu flach interpretiert und eine Alternative ohne Einbeziehung der sozialen Situation. Der Test besteht aus 45 Items, die sich in verschiedene mentale Zustände aufteilen lassen: Emotionen (Was fühlt Person NN?), Gedanken (Was denkt Person NN?), Absichten (Warum sagt/erzählt/fragt Person NN das?).

Es besteht nicht nur die Möglichkeit, den Test als Summe der richtigen Antworten (Gesamtscore) auszuwerten, sondern auch das Ergebnis nach den unterschiedlichen mentalen Zuständen aufzuteilen.

Nach Gabbard (2005) werden Hinweise auf den mentalen Zustand nicht nur über den Gesichtsausdruck, sondern auch über andere nonverbale Merkmale, sowie über den Tonfall übermittelt. Durch die lebensnahe Darstellung von sozialer Interaktion im MASC ist genau dies ermöglicht.

Abbildung 1: Beispielitem aus dem MASC

Anmerkung:
Klaus und Sandra scheinen sich zu amüsieren während Klaus von seinem Schwedenurlaub (1) erzählt. Als Michael hinzukommt, dominiert er sofort die Unterhaltung. Er spricht ausschließlich Sandra an (2). Ein bisschen von Michaels Geschichte gelangweilt, fragt Sandra Michael: „Warst Du eigentlich auch schon mal in Schweden?“ (3). Nach dem Betrachten der Szene werden die Patienten gebeten folgende Frage zu beantworten: „Warum fragt Sandra das?“ (4). Die richtige Antwort ist: a. Um Klaus in das Gespräch zu integrieren.

Der MASC zeigte eine hohe Interrater-Reliabilität (ICC = 0, 99), und hohe Re-Test-Reliabilität (r = 0, 97) (Dziobek et al., 2006). Der MASC wurde als Maß für kognitive Empathie in zwei der hier vorgestellten Studien eingesetzt (in **Publikation A;** Preißler et al., 2010, sowie in **Publikation C;** Ritter et al., 2011). In beiden zeigte der MASC eine gute interne Konsistenz (**Publikation A**: $\alpha = 0, 86$; **Publikation C**: $\alpha = 0, 80$).

Die beiden bisher vorgestellten Maße dienen zur Erfassung von nur einer Facette von Empathie, nämlich kognitiver Empathie. Da Empathie hier als multidimensionales Konstrukt verstanden wird, wurde angestrebt beide Facetten von Empathie möglichst simultan zu erfassen. Derzeit gibt es nur zwei Maße zur gleichzeitigen Erfassung von kognitiver und emotionaler Empathie. Auf diese wird im Folgenden eingegangen.

3.2.3 Der Interpersonal Reactivity Index

Der IRI (Davis, 1983) ist ein Selbstauskunftsinstrument zur Erfassung beider Facetten von Empathie. Er besteht aus vier Subskalen, wovon zwei der kognitiven Empathie (perspective taking, fantasy) und zwei der emotionalen Empathie (empathic concern, distress) zugeordnet werden. Der Fragebogen zeigte eine gute Konstruktvalidität (Davis, 1983).
Der IRI wurde in **Publikation B** (Dziobek et al., 2011) und in **Publikation C** (Ritter et al., 2011) verwendet.

3.2.4 Der Multifaceted Empathy Test

Der MET (Dziobek et al., 2008) ist ein neues, objektives und ökologisch valides Testverfahren zur simultanen Erfassung kognitiver und emotionaler Empathie. Die wesentlichen Vorteile im Vergleich zu den derzeit eingesetzten Instrumenten (d. h. Fragebögen; z. B. IRI (Davis, 1983), Empathy Quotient (Baron-Cohen & Wheelwright, 2004), Hogan Empathy Scale (Hogan, 1969)) sind geringere Anforderungen an Abstraktions- und Introspektionsfähigkeit sowie eine geringere Wahrscheinlichkeit für sozial erwünschte Antworten. Die Durchführung beinhaltet das Ansehen von Bildern, die Personen in Gemütszuständen negativer (z. B. elend) und positiver Valenz (z. B. liebevoll) zeigen. Der Proband ist zunächst aufgefordert, den mentalen Zustand der Person zu bestimmen (kognitive Empathie). Anschließend soll die Versuchsperson angeben, wie gelassen/erregt (Arousal, Ausmaß psychologischer Involviertheit) sie beim Betrachten des Bildes ist (emotionale Empathie, implizit gemessen). Danach soll sie angeben, wie besorgt sie um die dargestellten Personen ist bzw. wie sehr sie sich für die dargestellte Personen freut (emotionale Empathie, explizit gemessen) (siehe Abbildung 2). Die hier eingesetzte Version (METcore) besteht aus je 20 Bildern positiver und negativer Valenz (Kirchner, Hatri, Heekeren & Dziobek, 2011). Der MET kam sowohl in **Publikation B** (Dziobek et al., 2011) als auch in **Publikation C** (Ritter et al., 2011) zur Anwendung.

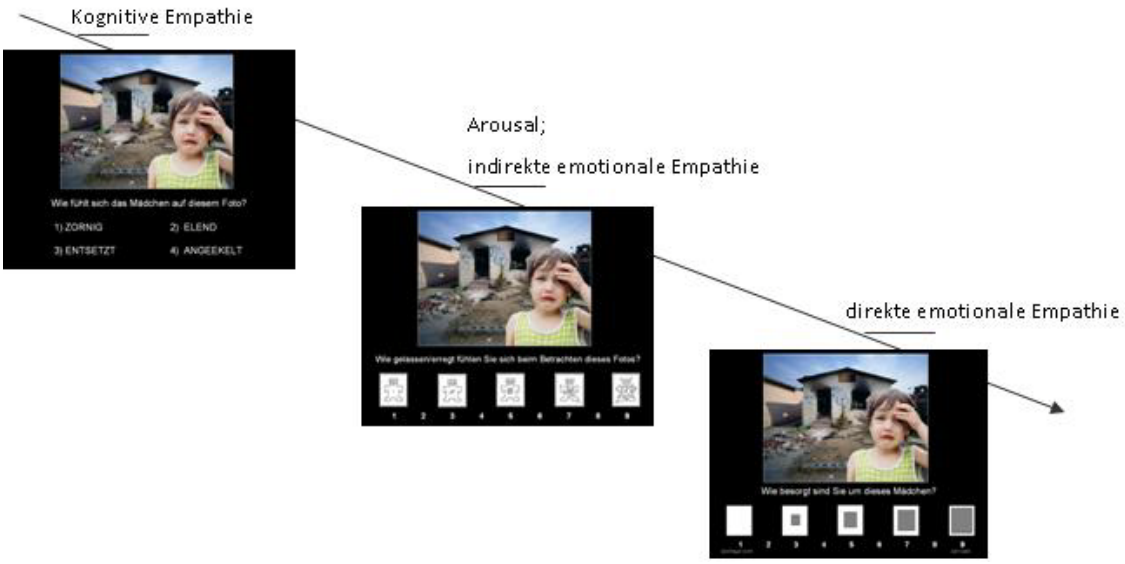

Abbildung 2: Beispielitem aus dem MET

Anmerkung

:Die Graphik stellt ein Beispielitem aus dem MET dar. Nach der Beantwortung der Frage „Was fühlt die Person?“ (kognitive Empathie) wird das Arousal über die Frage „Wie gelassen oder erregt sind Sie beim Betrachten dieses Fotos?“ erfasst. Als letztes Item wird die emotionale Empathie direkt erfasst über die Frage: „Wie besorgt sind Sie um die Person?“. Die Items zu einer Person kommen zeitlich immer hintereinander sowie in der hier dargestellten Reihenfolge.

3.3 Fazit

Empathie wird als multidimensionales Konzept verstanden. In den hier vorgestellten Studien wird versucht beide Facetten von Empathie, die kognitive und die emotionale, sowohl mit neuen, ökologisch validen (MET, MASC) als auch mit klassischen Erhebungsmethoden (RME, IRI) zu erfassen.

4. Empathie bei Personen mit Borderline-Persönlichkeitsstörung

4.1 Bisheriger Stand der Forschung

Personen mit BPS berichten über große Probleme in zwischenmenschlichen Beziehungen. Ihre unangebrachten emotionalen Reaktionen könnten Hinweise auf Probleme bei der Interpretation von Emotionen, Gedanken und Absichten anderer (kognitive Empathie) sowie ihrer emotionalen Reaktion darauf (emotionale Empathie) sein.

Hinweise für veränderte kognitive empathische Fähigkeiten bei Patienten mit BPS lassen sich aus verschiedenen Untersuchungen herleiten. In den meisten Studien sollen Emotionen aus Gesichtsausdrücken ohne sozialen Kontext erkannt werden (Donegan et al., 2003; Levine, Marziali & Hood, 1997; Lynch et al., 2006) (für einen systematischen Überblick siehe Domes et al., 2009). Je nach Fragestellung und Erhebungsinstrument zeigt sich ein anderes Bild: Patienten mit BPS waren entweder schlechter in der Erkennung negativer Emotionen (Levine et al., 1997), schlechter im Erkennen neutraler Emotionen (Donegan et al., 2003) oder Patienten mit BPS waren schneller in der Emotionserkennung (Lynch et al., 2006). In Studien, in denen keine Zeitbeschränkung oder andere konfundierende Variablen vorhanden sind, scheinen Patienten mit BPS im Durchschnitt genauso gut abzuschneiden, wie gesunde Kontrollpersonen (Domes et al., 2009).

Dennoch zeigt eine Studie (Minzenberg, Poole & Vinogradov, 2006), die sich nicht nur auf Emotionserkennung aus Gesichtern beschränkt, Probleme von Patienten mit BPS verglichen mit Kontrollprobanden. Es wurde bei 43 Patienten mit BPS und 27 Kontrollpersonen die Fähigkeit zur Integration von emotionalen Informationen verschiedener Ebenen (Gesichtsausdruck und Prosodie) untersucht. Patienten mit BPS waren erst dann schlechter im Erkennen von Emotionen, als sie Gesichtsausdruck und Prosodie integrieren sollten (Minzenberg et al., 2006). Aus diesem Ergebnis lässt sich vermuten, dass Patienten mit BPS größere Probleme mit komplexen emotionalen Stimuli als gesunde Personen haben.

Weitere Hinweise für einen Zusammenhang der BPS Symptomatik mit eingeschränkten sozial kognitiven Fähigkeiten, erfasst mit dem Adult Attachement Interview (de Haas, Bakermans-Kranenburg & van Ijzendoorn, 1994), lassen sich aus der Arbeit von Fonagy et al. (1996) herleiten. Auch Harari und Mitarbeiter berichten über eingeschränkte kognitive empathische Fähigkeiten bei

Patienten mit BPS verglichen mit gesunden Kontrollpersonen (Harari, Shamay-Tsoory, Ravid & Levkovitz, 2010). Sie erfassten kognitive Empathie mit dem IRI (Davis, 1983) und dem "Faux pas" task (Baron-Cohen, Jolliffe, Mortimore & Robertson, 1997) (Harari et al., 2010).

Auf der anderen Seite gibt es auch Untersuchungen, die keine Einschränkungen in ToM-Fähigkeiten bei Patienten mit BPS berichten (Arntz, Bernstein, Oorschot & Schobre, 2009; Fertuck et al., 2009). Die Arbeitsgruppe um Arntz (2009) fand in Ihrer Studie vergleichbare ToM-Fähigkeiten bei Patienten mit BPS und gesunden Kontrollpersonen im „advanced theory of mind task" (Happé, 1994). Fertuck und Mitarbeiter (2009) berichteten sogar über bessere Fähigkeiten von Patienten mit BPS verglichen mit gesunden Kontrollpersonen beim Erkennen mentaler Zustände im RME (Baron-Cohen et al., 2001).

Trotz der uneinheitlichen Befundlage werden Einschränkungen in sozial-kognitiven Fähigkeiten als ein Hauptcharakteristikum von BPS gesehen (Fonagy & Bateman, 2008). Es gibt sogar eine effektive Therapierichtung, „mentalization based" Therapie, die darauf abzielt, die sozial kognitiven Fähigkeiten der Patienten zu verbessern (Fonagy & Bateman, 2008).

Neben den Hinweisen zu Einschränkungen in kognitiver Empathie zeigen sich auch in emotionaler Empathie Unterschiede im Vergleich von Patienten mit BPS und gesunden Kontrollpersonen. Emotionale Empathie wurde bei Patienten mit BPS als emotionale Reaktion auf emotionsinduzierende Stimuli in Form von Selbstratings (Herpertz, Kunert, Schwenger & Sass, 1999; Herpertz et al., 2000; Levine et al., 1997), Videoaufzeichnung der emotionalen Reaktion im Gesicht (Renneberg, Heyn, Gebhard & Bachmann, 2005) und von körperlichem Arousal (u.a. Hautleitfähigkeit; Herpertz et al., 1999; Herpertz et al., 2000) erfasst.

Bei der Konfrontation mit emotionsinduzierenden Videosequenzen zeigten 30 Patienten mit BPS verglichen mit 30 gesunden Kontrollpersonen valenzunabhängig einen reduzierten emotionalen Gesichtsausdruck (Renneberg et al., 2005). Die gleichen körperlichen Reaktionen auf emotionsauslösende Bilder (IAPS; Lang, Bradley & Cuthbert, 1999) wie 27 gesunden Kontrollpersonen zeigten 27 Patienten mit BPS bei Emotionen negativer Valenz. Bei Emotionen positiver Valenz fand sich bei der gleichen Patientengruppe ein verzögerter Herzschlag. Diese Ergebnisse spiegeln sich auch in den Selbsteinschätzungen der Patienten wider (Herpertz et al., 1999; Herpertz et al., 2000). Im Gegensatz zu dieser Studie stehen Ergebnisse einer Untersuchung, in der man 30 Patienten mit BPS und 40 gesunde Kontrollpersonen mit negativen emotionalen Gesichtsausdrücken konfrontierte. Hier schätzten die Patienten mit BPS ihre emotionale Reaktion als intensiver ein (Levine et al., 1997).

Zusammenfassend gibt es Hinweise auf Einschränkungen von BPS Patienten in sowohl kognitiver als auch emotionaler Empathie. Die Befundlage ist allerdings uneinheitlich. Probleme scheinen sich vor

allem dann zu zeigen, wenn die Situationen oder Untersuchungsbedingungen alltagsnäher bzw. ökologisch valider werden.

Daher wurden in drei Studien Patienten mit BPS (**Publikation A**, **Studie 1 von Publikation B** und **Publikation C**) vorerst auf der Verhaltensebene untersucht, um das empathische Muster von Patienten mit BPS näher zu erfassen.

4.2 Untersuchungen zu Empathie auf Verhaltensebene

Publikation A

In der ersten der hier vorgestellten Studien lag der Fokus auf kognitiver Empathie bei Patienten mit BPS. Es wurden 64 Patientinnen mit BPS und 38 gesunde Kontrollpersonen untersucht. Alle Studienteilnehmer führten den RME (siehe Kapitel 3.2.1; Baron-Cohen et al., 2001) und den MASC (siehe Kapitel 3.2.2; Dziobek et al., 2006) durch.

Um den Unterschied zwischen den beiden Untersuchungsgruppen zu betrachten, wurde eine einfaktorielle ANOVA für den RME berechnet. Beide Gruppen unterschieden sich hierbei nicht voneinander ($F(1, 93) = 0, 30$, $p = 0, 588$). Für den MASC-Gesamtscore ($F(1, 102) = 17, 56$, $p < 0, 001$) und die MASC-Subscores (siehe Tabelle 2, Preißler et al., 2010) zeigte sich allerdings ein anderes Bild. Patienten mit BPS waren im Erkennen von Gefühlen, Gedanken und Absichten im MASC schlechter als die gesunden Kontrollprobanden.

Die Ergebnisse im RME weisen in die gleiche Richtung wie bisherige Studien, die keinerlei Einschränkungen bei BPS Patienten in reinen Emotionserkennungsaufgaben berichteten (Domes et al., 2009). Die Ergebnisse im ökologisch valideren MASC unterstützen allerdings die These, dass Patienten mit BPS Probleme haben, wenn es sich um soziale Integrationsaufgaben höherer Ordnung handelt und nicht nur basale Emotionserkennung.

Zur differenzierten weiteren Betrachtung dieser Ergebnisse wurde der Einfluss von Posttraumatischer Belastungsstörung (PTBS) auf sozial kognitive Fähigkeiten bei Patienten mit BPS untersucht (siehe hierzu Kapitel 5.1.).

Publikation B

Publikation B (Dziobek et al., 2011) besteht aus zwei empirischen Arbeiten. Die erste ist eine Verhaltensstudie. Sie konzentriert sich auf vermutete Einschränkungen in kognitiver und emotionaler Empathie bei Patientinnen mit BPS. Empathie wird hierbei sowohl über den IRI (siehe Kapitel 3.2.3; Davis, 1983) als auch über den MET (siehe Kapitel 3.2.4; Dziobek et al., 2008) als multidimensionales Konzept erfasst. Im zweiten Teil von **Publikation B** wird eine Studie dargestellt, die die neuronalen

Korrelate von Empathie an einer unabhängigen Stichprobe von Patienten mit BPS untersucht. **Studie 2 von Publikation B** wird erst im weiteren Verlauf (siehe Kapitel 6.3.2) diskutiert.

In **Studie 1 von Publikation B** wurden auf der Verhaltensebene 21 Patientinnen mit BPS mit in Alter und IQ parallelisierten gesunden Kontrollprobandinnen verglichen. Die Patientinnen zeigten einen Trend zu Einschränkungen auf den emotionalen und kognitiven Skalen des IRI (Davis, 1983) verglichen mit den gesunden Kontrollpersonen. Im objektiveren und ökologisch valideren Verfahren, dem MET (Dziobek et al., 2008; Kirchner et al., 2011), zeigten die Patienten signifikante Einschränkungen in sowohl kognitiver Empathie ($t(40) = 2, 12$, $p = 0, 03$) als auch emotionaler Empathie ($t(40) = 2, 22$, $p = 0, 04$).

Patienten mit BPS könnten in ihrer Fähigkeit Selbsteinschätzungsfragebögen, wie den IRI (Davis, 1983), korrekt auszufüllen, eingeschränkt sein. Denn dies verlangt eine gute Introspektionsfähigkeit von den Probanden und Patienten mit BPS haben lediglich eingeschränkte Fähigkeit zur Introspektion (Levine et al., 1997). Das ist eine mögliche Ursache für den fehlenden Gruppenunterschied zwischen Patienten mit BPS und gesunden Kontrollpersonen im IRI (Davis, 1983). Der fotorealistische MET (Dziobek et al., 2008) ist weniger abstrakt und vermeidet damit mögliche konfundierende Probleme wie die potenzielle mangelnde Introspektionsfähigkeit der Patienten mit BPS.

Patienten zeigen auf der Verhaltensebene in **Publikation B** (Dziobek et al., 2011), wie auch schon in **Publikation A** (Preißler et al., 2010), Einschränkungen in kognitiver Empathie. Gleichzeitig konnten in **Studie 1 von Publikation B** auch Einschränkungen in emotionaler Empathie bei Patienten mit BPS festgestellt werden.

Publikation C

Das Hauptaugenmerk dieser Publikation ist Empathie bei Narzisstischer Persönlichkeitsstörung (NPS). Diese ist wie BPS im DSM IV-TR im Cluster B von Achse II eingeordnet (American Psychiatric Association, 2000). Da beide Störungen ein sehr ähnliches Muster an Symptomen und Komorbiditäten aufweisen (Ritter et al., 2010), wird hier NPS von BPS abgegrenzt. Auch wenn **Publikation C** eine Verhaltensstudie ist, werden die Studie und die wesentlichen Ergebnisse im Kapitel 5.2 vorgestellt, in dem versucht wird, die empathischen Muster von Patienten mit BPS im Vergleich zu Patienten mit NPS darzulegen.

4.3 Fazit

In den vorgestellten Studien (**Publikation A, Studie 1 von Publikation B** und **Publikation C**) konnte gezeigt werden, dass Patientinnen mit BPS Defizite in kognitiv empathischen Prozessen und erniedrigte emotionale Empathie aufweisen.

5. Komorbiditäten und deren mögliche Einflüsse auf die empathische Leistung

Borderline Persönlichkeitsstörung ist eine Störung mit vielen Komorbiditäten (McGlashan et al., 2000; Morey, 1988; Zanarini et al., 1998; Zanarini, Frankenburg, Hennen, Reich & Silk, 2004). Daher wurde im weiteren Verlauf der Frage nachgegangen, ob die gefundenen Einschränkungen in empathischen Prozessen BPS spezifisch sind oder ob diese durch eine komorbid auftretende Störung erklärt werden können. Dazu wurden zwei verschiedene Komorbiditäten näher untersucht, zum einen die PTBS (**Publikation A**; Preißler et al., 2010 und **Manuskript A**), zum anderen NPS (**Publikation C**; Ritter et al., 2011).

In bis zu 58 % der Patienten mit BPS wird zusätzlich eine PTBS diagnostiziert (Zanarini et al., 1998; Zanarini et al., 2004). Außerdem ist BPS mit traumatischen Kindheitserfahrungen (insbesondere sexueller Missbrauch) assoziiert (Lobbestael, Arntz & Bernstein, 2010). Gleichzeitig ist eine komorbid auftretende PTBS ein Faktor, der eine negative Prognose für den Verlauf der Störung darstellt (Zanarini, Frankenburg, Hennen, Reich & Silk, 2006). BPS Patienten, die unter Intrusionen leiden, weisen oft eine PTBS oder eine subsyndromale PTBS auf (Harned, Rizvi & Linehan, 2010).

Die Diagnosen NPS und BPS werden in klinischen Stichproben bis zu 50 % als gegenseitige Komorbiditäten vergeben (Morey, 1988; Westen, Shedler & Bradley, 2006). Zusätzlich gibt es große Überschneidungen in der beschriebenen Symptomatik, wie bei Problemen mit der Affektregulation, Impulsivität und instabilen Beziehungen (Blais, Hilsenroth & Castlebury, 1997; Morey, 1988; Ronningstam & Gunderson, 1991). Beide Persönlichkeitsstörungen werden derzeit im Cluster B der Achse II des DSM IV-TR (American Psychiatric Association, 2000) diagnostiziert. Sie haben neben ihrer diagnostischen Nähe eine starke Ähnlichkeit hinsichtlich ihrer Komorbiditäten (Ritter et al., 2010).

5.1 Posttraumatische Belastungsstörung

Nicht nur die hohe Komorbidität von PTBS bei Patienten mit BPS ist ausschlaggebend für die Untersuchung des Einflusses dieser Störung auf die empathischen Fähigkeiten von Patienten mit BPS, sondern auch Ergebnisse aus Emotionserkennungsstudien, die daraufhinweisen, dass intrusive Symptome und eine komorbid auftretende PTBS negative Prädiktoren für Emotionserkennungsfähigkeiten bei Patienten mit BPS sind (Dyck et al., 2009).

Der potenzielle Einfluss von PTBS oder subsyndromaler PTBS auf die empathischen Fähigkeiten von Patienten mit BPS wurde in **Publikation A** (Preißler et al., 2010) auf der Verhaltensebne untersucht. Die Gruppe der 64 Patientinnen mit BPS unterteilt sich in Patienten mit komorbider PTBS (N = 22) und Patientinnen ohne zusätzlich auftretende PTBS (N = 42). Bei beiden Patientengruppen wurde die Stärke der berichteten BPS Symptomatik mit der „Borderline Symptom List“ (BSL; Bohus et al., 2007)

erhoben. Außerdem haben wir die traumatischen Erfahrungen der Patienten mit der „Posttraumatischen Diagnose Skala“ (PDS; Foa, 1995) quantifiziert.

Um explorativ abzuklären, welche Subsyndrome von BPS, erfasst über die BSL Subskalen (Bohus et al., 2007), einen möglichen zusätzlichen Erklärungshinweis für die gefundenen Einschränkungen in sozialer Kognition liefern (siehe Kapitel 4.2), wurden vier schrittweise vorwärtsgerichtete lineare Regressionen durchgeführt. Nur die Subskala „Intrusion” konnte einen signifikanten Beitrag zur Erklärung für die MASC Subskala „Gedanken” liefern (R^2 = 0, 09, F = 6, 20, p = 0, 015; β = -0, 35, t = -2, 50).

Außerdem wurde der Einfluss komorbid auftretender Störungen (Majore Depression, Substanzmissbrauch, Essstörung, PTBS, weitere Persönlichkeitsstörungen) untersucht. Dazu führten wir wieder vier schrittweise vorwärtsgerichtete lineare Regressionen durch. Wieder ergab nur ein Modell ein signifikantes Ergebnis. Nur eine zusätzliche Diagnose einer PTBS leistete einen signifikanten Beitrag, auch hier zur Erklärung der MASC Subskala “Gedanken” (R^2 = 0, 13, F = 9, 35, p = 0, 003; β = -0, 69, t = -3, 06).

Neben diesen Hinweisen auf den Einfluss von PTBS auf sozial-kognitive Fähigkeiten gingen wir der Frage nach, ob die Art des berichteten traumatischen Ereignisses, erfasst über die PDS, die gefundenen Einschränkungen in sozialer Kognition vorhersagen kann. Sexuelle Übergriffe aus dem Bekanntenkreis war hier der Prädiktor mit signifikantem Einfluss auf den MASC Summensore (R^2 = 0, 086, F = 5, 82, p = 0, 019; β = -4, 61, t = -2, 41).

5.2 Narzisstische Persönlichkeitsstörung

Publikation C (Ritter et al., 2011) richtete ihren Fokus auf Empathie bei NPS. Da diese Persönlichkeitsstörung bereits in ihren diagnostischen Kriterien einen „Mangel an Empathie“ beschreibt, war der Fokus dieser Untersuchung neben der Abgrenzung von BPS auch die Überprüfung dieses Diagnosekriteriums.

In der Studie wurde Empathie sowohl mit dem MET (siehe Kapitel 3.2.4; Dziobek et al., 2008), dem IRI (siehe Kapitel 3.2.3; Davis, 1983) als auch mit dem MASC (siehe Kapitel 3.2.2; Dziobek et al., 2006) erfasst. Um die Spezifität des Merkmals „Mangel an Empathie“ zu prüfen, wurden 47 Patienten mit NPS, 27 Patienten mit BPS (ohne komorbide NPS) und 53 gesunde Kontrollpersonen untersucht. Patienten mit NPS und zusätzlich auftretender BPS wurden aus den dazu durchgeführten Analysen ausgeschlossen, um Patienten mit BPS und Patienten mit NPS vergleichen zu können.

Im IRI (Davis, 1983) zeigte sich ein signifikanter Effekt für den Gruppenfaktor (λ = 0, 902, F(4, 188) = 2, 50, p = 0, 044) bei einer MANOVA für die Subskalen „empathic concern“ und „perspective taking“, wobei die apriori Kontraste Hinweis darauf geben, dass bei „perspective taking“

sowohl Patienten mit NPS als auch Patienten mit BPS niedrigere Ausprägungen verglichen mit gesunden Kontrollprobanden haben. Bei der Subskala für emotionale Empathie, „empathic concern", geht der Effekt allein auf niedrige Werte der Patienten mit BPS zurück.

Auch für den MASC Gesamtscore als abhängige Variable und das Geschlecht als Kovariate gab es einen signifikanten Gruppeneffekt ($F(2, 95) = 3{,}53$, $p = 0{,}033$). Die apriori Kontraste wiesen hier allerdings nur auf einen signifikanten Unterschied zwischen Patienten mit BPS und gesunden Kontrollpersonen hin ($p = 0{,}011$). Dies deutet auf keine veränderten kognitiv empathischen Fähigkeiten der Patienten mit NPS hin.

Auch die MANOVA, die die MET Subskalen als unabhängige Variablen betrachtete, ergab einen signifikanten Effekt von Gruppe ($\lambda = 0{,}762$, $F(6, 182) = 4{,}42$, $p < 0{,}001$). Nur bei kognitiver Empathie unterschieden sich Patienten mit BPS signifikant von Patienten mit NPS ($p = 0{,}022$).

Für die apriori Kontraste der emotionalen Empathieskalen unterschieden sich beide Patientengruppen signifikant von der Kontrollgruppe, aber nicht signifikant voneinander (siehe Tabelle 3, **Publikation C**; Ritter et al., 2011).

Patienten mit BPS ohne NPS zeigten im Gegensatz zu Patienten mit NPS Einschränkungen in kognitiver Empathie im MASC und einen Trend zu Einschränkungen im MET. In emotionaler Empathie wurden jedoch Einschränkungen für beide Patientengruppen gefunden.

5.3 Fazit

Die dargestellten Studien liefern Hinweise darauf, dass Patienten mit BPS sowohl in kognitiver als auch in emotionaler Empathie Einschränkungen haben. Diese Defizite scheinen durch eine komorbide Achse I Störung (PTBS) verstärkt zu werden. Es konnte gezeigt werden, dass drei Faktoren zu eingeschränkten kognitiv empathischen Fähigkeiten bei den Patienten beitragen: intrusive Symptomatik, komorbide PTBS und sexuelle Übergriffe durch eine Person aus dem Familien- oder Bekanntenkreis. Da intrusive Symptome ein wesentliches Merkmal von PTBS sind, deuten diese Ergebnisse auf den negativen Einfluss von PTBS auf sozial kognitive Fähigkeiten der Patienten mit BPS hin.

Weitere Forschung sollte hier auch andere mögliche Komorbiditäten, die auf Grund ihrer geringen Fallzahl in diesen Stichproben keinen Einfluss aufzeigen konnten, näher untersuchen. Betrachtet man die komorbid auftretenden Störungen bei BPS, gibt es neben den diskutierten Ergebnissen zu PTBS u.a. auch Hinweise darauf, dass Essstörungen, speziell Anorexia Nervosa, mit starken Einschränkungen in kognitiver Empathie, ToM bzw. sozialer Kognition einhergehen (u.a. Russell, Schmidt, Doherty, Young & Tchanturia, 2009; Tchanturia et al., 2004; Zucker et al., 2007). In der akuten Phase dieser Störung könnte dies auch eine reine Folge des Hungerns auf das Gehirn

darstellen. Ein Viertel der Patienten in **Publikation A** (Preißler et al., 2010) litt unter einer akuten Essstörung. Dennoch konnte eine zusätzlich auftretende Essstörung keinen weiteren Beitrag zur Erklärung der Probleme der Patienten mit BPS in kognitiver Empathie liefern. Bei näherer Betrachtung der Daten könnte dies daran liegen, dass nur eine Patientin eine akute Anorexia Nervosa hatte. 15 Patientinnen dieser BPS Stichprobe litten unter einer Bulimia Nervosa. Dennoch ist die in **Publikation A** (Preißler et al., 2010) beschriebene Stichprobe repräsentativ für BPS. Denn Bulima Nervosa kommt bei Patienten mit BPS häufiger vor als Anorexia Nervosa (Zanarini et al., 1998). Man kann anhand der Ergebnisse von **Publikation A** (Preißler et al., 2010) nicht ausschließen, dass auch eine zusätzlich auftretende Anorexia Nervosa einen verschlechternden Effekt auf die empathischen Leistungen der Patienten mit BPS hat.

Außerdem konnte gezeigt werden, dass die Einschränkungen in kognitiver Empathie nicht bei Patienten mit NPS, sondern nur bei Patienten mit BPS auftreten. Aber Patienten mit beiden Störungen (also entweder mit NPS oder mit BPS) weisen Probleme in emotionaler Empathie auf (Ritter et al., 2011). Damit kann man das „empathische Muster“ von Patienten mit BPS von dem der Patienten mit NPS (Ritter et al., 2011) aber auch von dem der Patienten mit Psychopathie abgrenzen. Bei Patienten mit Psychopathie, genau wie bei Patienten mit NPS, ist der Mangel an Empathie ein wesentliches Diagnosekriterium (Blair, 2005a; Goldberg et al., 2007; Wiehe, 2003). Aber genau wie NPS ist Psychopathie mit Einschränkungen in emotionaler Empathie (Blair, 2005a; Goldberg et al., 2007; Ritter et al., 2011) und nicht mit Einschränkungen in kognitiver Empathie (Dolan & Fullam, 2004; Richell et al., 2003) verbunden.

Neben der Abgrenzung von anderen Persönlichkeitsstörungen ist das „empathische Muster“ von Patienten mit BPS aber auch von den klassisch berichteten Problemen von Patienten des Autismusspektrums unterscheidbar. Im Gegensatz zu BPS Patienten weisen Patienten mit einer Autismusspektrumsstörung weitestgehend intakte emotionale empathische Fähigkeiten auf. Patienten dieser Störungsgruppe leiden hauptsächlich unter Einschränkungen in kognitiver Empathie (Dziobek et al., 2008).

6. Neuronale Korrelate

Das folgende Kapitel stellt neuronale Netzwerke für kognitive und emotionale Empathie vor, befasst sich mit den neuronalen Korrelaten von BPS und kombiniert beides, um zu demonstrieren, dass bestimmte funktionale und anatomische störungsspezifische Veränderungen durchaus veränderte empathische Fähigkeiten, oder umgekehrt, bedingen können.

6.1 Empathie

Wie bereits beschrieben (siehe Kapitel 3), wird Empathie in den hier dargestellten Studien als multidimensionales Konstrukt betrachtet. Beide Facetten von Empathie wurden bereits mehrfach, aber immer getrennt voneinander, mit Verfahren funktioneller Bildgebung untersucht. Für kognitive Empathie, Mentalizing oder ToM wird ein Netzwerk diskutiert, das aus dem medial präfrontalen Kortex (mPFC) (im Besonderen anterior cingulärer Kortex (ACC))[1], der Schnittstelle zwischen temporalen und parietalen Regionen („temporo-pariatal junction (TPJ)“)[2], die sich ausdehnt in den superior temporalen Sulcus (STS), und aus Bereichen des inferioren Parietallappens und den temporalen Polen[3] besteht (Blair, 2005b; Frith & Frith, 2006; Völlm et al., 2006).
Emotionale Empathie scheint ein Netzwerk zu aktivieren, das ähnliche Areale einbezieht, die auch beim Empfinden von eigenen Emotionen aktiv sind (Blair, 2005b; Singer, 2006). Unabhängig von der Valenz der Emotion werden bei Emotionsempfindung der STS und limbische Strukturen aktiviert (Blair, 2005b). Zu den aktivierten limbischen Bereichen zählen u.a. die Amygdala und vor allem der anteriore insuläre Kortex (IC). Der anteriore Bereich des IC wurde in verschiedenen Untersuchungen als wesentlicher Teil eines Netzwerkes identifiziert, das Emotionserkennung und Nachfühlen von Emotionen anderer im sozialen Kontext vermittelt (Fan, Duncan, de Greck & Northoff, 2011; Lamm, Decety & Singer, 2011; Singer, Critchley & Preuschoff, 2009).

6.2 Patienten mit Borderline Persönlichkeitsstörung

Patienten mit BPS weisen verglichen mit gesunden Kontrollpersonen, eine Reihe struktureller und funktioneller Unterschiede in den limbischen und präfrontalen Regionen (v.a. Amygdala,

[1] Für eine ausführliche Diskussion der Rolle dieser Region für kognitive Empathie wird auf die Metaanalyse von Seitz und Kollegen (2006) sowie die Überblicksarbeit von Amodio und Frith (2006) verwiesen.

[2] Die Rolle des TPJ für Empathie wird in der Metanalyse von Decety und Lamm (2007) ausführlich diskutiert.

[3] Für eine ausgiebige Diskussion der Funktion des temporalen Pols siehe Olson und Kollegen (2007).

orbitofrontaler Kortex (OFC) und ACC) auf, die eine Rolle in den genannten Netzwerken von kognitiver und emotionaler Empathie spielen (Brendel, Stern & Silbersweig, 2005; Lis, Greenfield, Henry, Guile & Dougherty, 2007; Schmahl, McGlashan & Bremner, 2002).

6.2.1 Funktionelle Befunde

Um borderline-typische neuronale Korrelate zu erfassen, sind bisher im fMRT unterschiedlichste Untersuchungsmaterialien verwendet worden: standardisierte emotionale Stimuli meist aus dem „International Affective Picture System“ (IAPS; Lang et al., 1999), standardisierte Aufnahmen von Gesichtern, wie die „Ekman Faces“ (Ekman, 1993), oder personalisierte autobiographische Skripte.
Bei der Verwendung von negativem emotionalen Bildmaterial der IAPS zeigte sich in der Studie von Herpertz und Mitarbeitern erhöhte Aktivität in der Amygdala bei sechs Patienten mit BPS verglichen mit gesunden Kontrollpersonen (Herpertz et al., 2001).
Die Arbeitsgruppe um Donegan verwendete die „Ekman-Faces“ (Donegan et al., 2003). Sie untersuchten Patienten mit BPS mit und ohne komorbider PTBS. Für beide Gruppen fanden die Autoren differenzierte Effekte. Patienten mit PTBS zeigten linkshemisphärisch eine Hyper-Reaktivität der Amygdala. Im Gegensatz hierzu wiesen Patienten mit BPS ohne PTBS beidseitig eine Hyper-Reaktivität der Amygdala auf. Auch im cingulären Kortex fanden sich differenzierte Effekte für beide Patientengruppen. Patienten mit BPS und komorbider PTBS zeigten bei der Konfrontation mit ängstlichen Gesichtern Deaktivierung im cingulären Kortex. Dieser Effekt trat nicht bei Patienten mit BPS ohne PTBS auf. Im präfrontalen Kortex zeigte sich ein gegenteiliges Aktivierungsmuster. Patienten mit BPS ohne PTBS zeigten Deaktivierung. Diese blieb bei Patienten mit BPS und komorbider PTBS aus.
Eine weitere Möglichkeit zur Erfassung borderline-typischer Korrelate mit funktioneller Bildgebung ist die Verwendung von personalisierten Skripten traumatischer Ereignisse. In einer PET Studie wurde unter Verwendung von personalisierten Skripten zu Kindheitsmissbrauch bei Frauen ohne BPS erhöhte Aktivität im ACC und im linken OFC gefunden. Außerdem zeigten die Kontrollpersonen hier eine reduzierte Aktivierung im linken dorsolateralen präfrontalem Kortex (DLPFC). Dieses traumaspezifische Aktivierungsmuster von ACC, OFC und DLPFC blieb bei Frauen mit BPS aus (Schmahl, Vermetten, Elzinga & Bremner, 2004).
In einer weiteren Untersuchung wurden neuronale Korrelate von traumatischen versus aversiven, dabei aber nicht traumatischen, Erinnerungen bei Patienten mit BPS mit und ohne komorbider PTBS verglichen (Driessen et al., 2004). Patienten mit BPS und komorbider PTBS wiesen im OFC beidseitig eine breit gestreute Aktivierung auf. Patienten mit BPS ohne PTBS zeigten nur minimale Aktivierung im OFC.

Neben diesen Studien zu funktionellen Auffälligkeiten gibt es einige Untersuchungen, die sich dem Volumen verschiedener Hirnbereiche widmen und über anatomische Auffälligkeiten bei Patienten mit BPS berichten.

6.2.2 Strukturelle Befunde

Magnet-Resonanz-Tomographie (MRT) basierte Untersuchungen des Hirnvolumens konzentrieren sich im Wesentlichen auf die Volumina von Hippocampus und Amygdala. Die Amygdala hat bei Patienten mit BPS verglichen mit gesunden Kontrollpersonen ein um bis zu 24 % reduziertes Volumen (Driessen et al., 2000; Nunes et al., 2009; Tebartz van Elst et al., 2003). In den gleichen Studien wurde ein bis zu 20, 5 % reduziertes Volumen des Hippocampus bei Patienten mit BPS im Kontrast zu gesunden Kontrollpersonen berichtet. Neben den Ergebnissen zu reduzierten Volumina gibt es aber auch Studien, die keine Unterschiede (New et al., 2007) oder sogar vergrößerte Volumina (Minzenberg, Fan, New, Tang & Siever, 2008) des Hippocampus verglichen mit gesunden Kontrollprobanden aufzeigen. Gleichzeitig wird in den genannten Studien die symptomatische Nähe von BPS zu PTBS erneut auffällig, da auch PTBS (siehe Kapitel 5.1) und Traumatisierung mit reduzierten Hippocampus- und Amygdalavolumina einhergehen (Karl et al., 2006).

Aber auch andere Strukturen weisen Auffälligkeiten auf. So findet man bei Patienten mit BPS im Vergleich zu gesunden Kontrollpersonen reduzierte Volumen des OFC. Auch der präfrontale Kortex (PFC), speziell der ACC, scheint verglichen mit gesunden Kontrollpersonen kleinere Volumina zu haben (Brunner et al., 2010; Minzenberg et al., 2008; Tebartz van Elst et al., 2003). Aber auch für diese Regionen gibt es Studien, die diese Ergebnisse nicht unterstützen (Brambilla et al., 2004; Rüsch et al., 2003). Wiederum sind die Ergebnisse schwer von Patienten mit PTBS abgrenzbar, da u.a. das Volumen des PFC auch bei dieser Patientengruppe reduziert ist (De Bellis et al., 2002).

Aus den hier skizzierten Ergebnissen geht hervor, dass man auf Grund der bisherigen Befundlage nicht klar zwischen PTBS Auswirkungen oder der Auswirkung von BPS auf die Anatomie des menschlichen Gehirns trennen kann. Demnach ist es nicht eindeutig, ob die gefundenen anatomischen Abweichungen auf BPS zurückgehen oder auf eine komorbide PTBS (siehe Kapitel 5.1).

Einen weiteren Hinweis auf die Notwendigkeit der Unterscheidung von BPS Patienten mit komorbider PTBS und ohne komorbide PTBS bei der Betrachtung anatomischer Veränderungen liefert eine Studie von Schmahl und Kollegen (Schmahl et al., 2009). Die Autoren teilten in ihrer Studie die BPS Patientengruppe (N = 25) in Patienten mit einer zusätzlich auftretenden PTBS (N = 10) und ohne zusätzlich auftretende PTBS (N = 15) ein. Sie stellten fest, dass nur Patienten mit komorbid auftretender PTBS kleinere Hippocampusvolumina als die gesunden Kontrollpersonen (N = 25) hatten.

6.2.3 Fazit

Bei Patienten mit BPS wurden bisher sowohl funktionelle als auch anatomische Unterschiede in Regionen gefunden, die man in die skizzierten Netzwerke von kognitiver und emotionaler Empathie (siehe Kapitel 6.1) einordnen kann. Allerdings geht aus den bisherigen Studien nicht hervor, ob diese funktionellen und anatomischen Auffälligkeiten durch BPS oder durch eine zusätzlich auftretende PTBS bedingt sind.

Daher wurde zuerst überprüft, ob die auf Verhaltensebene gefunden Einschränkungen in emotionaler und kognitiver Empathie (siehe Kapitel 4.2; **Publikation A, Studie 1 von Publikation B, Publikation C**) durch abweichende Aktivierungsmuster in den in Kapitel 6.1 skizzierten Netzwerken bedingt sind (siehe Kapitel 6.3.2; **Studie 2 von Publikation B;** Dziobek et al., 2011).

Da gezeigt werden konnte, dass eine zusätzlich auftretende PTBS die Einschränkungen in kognitiver Empathie bei der untersuchten Patientengruppe verstärkt (siehe Kapitel 5.1; **Publikation A;** Preißler et al., 2010), wurde anschließend die These überprüft, dass sich BPS Patienten mit PTBS in ihren neuronalen Korrelaten empathiespezifisch von Patienten mit BPS ohne komorbide PTBS unterscheiden (siehe Kapitel 6.3.4; **Manuskript A**).

Auch bei der Betrachtung anatomischer Daten scheint die Unterscheidung der Auswirkungen einer komorbiden PTBS auf Patienten mit BPS unumgänglich zu sein. Daher wurde zusätzlich der Frage nachgegangen, ob für BPS Patienten, unabhängig von einer komorbiden PTBS, anatomische Veränderungen verglichen mit gesunden Kontrollpersonen nachweisbar sind (siehe Kapitel 6.4; **Manuskript B**).

6.3 Untersuchung mit funktioneller Bildgebung

6.3.1 fMRT-Adapation des Multifaceted Empathy Test

Neuronale Korrelate von kognitiver und emotionaler Empathie sind bisher immer getrennt untersucht worden. Der in **Studie 1 von Publikation B** und in **Publikation C** auf Verhaltensebene eingesetzte MET (siehe Kapitel 3.2.4; Dziobek et al., 2008) bietet die Möglichkeit der gleichzeitigen Untersuchung kognitiver und emotionaler Facetten von Empathie. Daher wurde den Probanden in **Studie 2 von Publikation B** (Dziobek et al., 2011) und **Manuskript A** eine adaptierte Version des MET (Dziobek et al., 2008; Kirchner et al., 2011) im funktionellen Magnetresonanz-Tomographen (fMRT) präsentiert. Durch Maustastendruck sollte das im fMRT präsentierte Bild, das für 4,5 Sekunden erschien, bewertet werden. Im Präsentationszeitraum sollte die mit dem Bild eingeblendete Frage durch Maustastendruck beantwortet werden. Dabei sah der Proband immer zwei

Antwortalternativen zwischen denen er sich entscheiden sollte. Das Bild wurde jeweils dreimal dargeboten. Bei jedem Präsentationsblock stellte sich der Versuchsperson eine neue Aufgabe. Es sollte entweder entschieden werden, was die dargestellte Person fühlt (kognitive Empathie) oder ob man mit der dargestellten Person fühlt (emotionale Empathie), als Kontrollbedingung war das Alter / Geschlecht der abgebildeten Person einzuschätzen (siehe Abbildung 3).

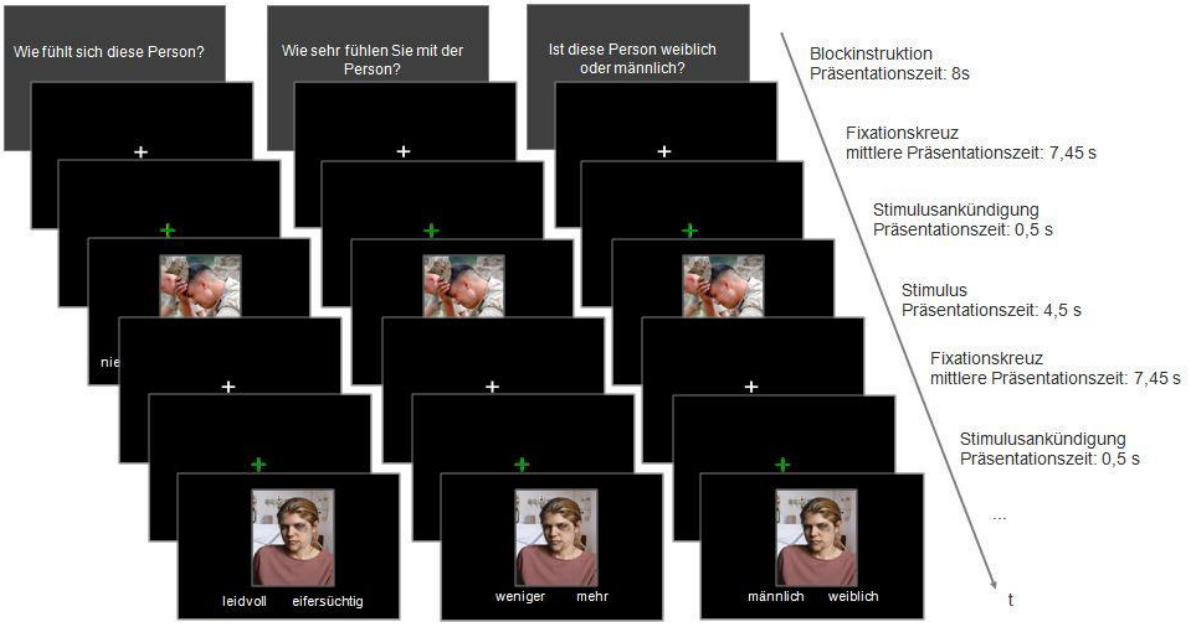

Abbildung 3: fMRT-Anpassung des MET

Anmerkung:
MET fMRI-Adaptation: Beispielitems für die drei unterschiedlichen MRT Bedingungen (kognitive Empathie: „Wie fühlt sich diese Person?“; emotionale Empathie: „Wie sehr fühlen Sie mit der Person“; Higher level baseline: „Ist diese Person weiblich oder männlich?“).

Um für die verschiedenen Bedingungen eine genügend große statistische Power zu haben, erfolgte für den MET eine Stimulusaufstockung, d.h. im Vergleich zum ursprünglichen Test besteht die fMRT-Version aus 40 statt 20 Bildern je Valenz. Die Darbietung erfolgte in 2 Durchgängen zu je 8 Blöcken (= Präsentationsbedingung). In jedem Block wurden 10 Bilder in pseudorandomisierter Reihenfolge dargestellt. Während der fMRT-Messung wurde als Indikator für implizite emotionale Empathie und Arousal die Hautleitfähigkeit der Versuchsperson abgeleitet.

Die Messung erfolgte an einem 1, 5 Tesla Siemens Sonata. Die T2*-Messung hatte 26 Schichten, 4 x 4 x 4 mm Voxelgröße, TR = 2, 5 s, TE = 40 ms; FoV = 256 mm. Zudem wurden zwei T1-gewichtete Messung (TR = 12, 24 min; FoV = 256 mm) durchgeführt.

6.3.2 Untersuchung neuronaler Korrelate von Empathie bei Patienten mit Borderline-Persönlichkeitsstörung

Wie bereits in Kapitel 4.2 dargestellt, besteht **Publikation B** (Dziobek et al., 2011) aus zwei voneinander getrennten Studien. Der erste Teil von **Publikation B** (Dziobek et al., 2011), die Verhaltensstudie, wurde bereits in Kapitel 4.2 beschrieben. Die zweite Untersuchung basiert im Wesentlichen auf den Ergebnissen der in Kapitel 4.2 dargestellten Verhaltensstudien. **Studie 2 von Publikation B** (Dziobek et al., 2011) ist eine fMRT-Studie zur Untersuchung der neuronalen Korrelate von Empathie bei Patienten mit BPS. Nach Abschluss der ersten Studie wurden weitere 30 Patientinnen mit BPS und eine dazu in Alter, IQ und Geschlecht parallelisierte Kontrollgruppe untersucht. Von den 30 Kontrollprobandinnen musste eine Teilnehmerin ausgeschlossen werden, da sie sich während der Messung stärker als 5 mm bewegte und dies nicht durch die dem Auswerteprogramm eigenen Algorithmen zur Bewegungskorrektur (FSL, FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl; Jenkinson, Bannister, Brady & Smith, 2002) korrigiert werden konnte. Die zweite Stichprobe an Patientinnen in **Publikation B** (Dziobek et al., 2011) unterschied sich hinsichtlich ihrer BPS-Symptomausprägung (erfasst über die BSL; Bohus et al., 2007) nicht von der Stichprobe auf der Verhaltensebene in dieser Publikation (siehe Kapitel 4.2). Die Teilnehmer der zweiten Teilstudie von **Publikation B** (Dziobek et al., 2011) mussten mindestens 14 Tage frei von jeglicher psychotroper Medikation sein. Die Studienteilnehmer haben im MRT eine fMRT angepasste Version des MET (siehe Kapitel 6.3.1; Dziobek et al., 2008; Kirchner et al., 2011) bearbeitet.

Während kognitiver Empathie zeigten Kontrollpersonen im Vergleich zu Patientinnen mit BPS eine höhere Aktivierung im linken posterioren STS (MNI Koordinaten des Peak Voxels: -58, -44, 8, z = 3, 11). Die Aktivierung in dieser Region wies einen negativen korrelativen Zusammenhang mit der Stärke der berichteten Intrusionen, erfasst über die BSL (Bohus et al., 2007) bei den Patienten mit BPS auf (r = -0, 42, p = 0, 02) (siehe Abbildung 2, Seite 7, **Publikation B**).

Unter der emotionalen Empathiebedingung zeigten Patientinnen mit BPS eine höhere BOLD Antwort sowohl im rechten IC (MNI Koordinaten des Peak Voxels: 34, -12, 14, z = 3, 14) als auch im rechten STS (MNI Koordinaten des Peak Voxels: 68, -28, 0, z = 3, 32). Innerhalb der Patientengruppe korreliert die Veränderungen im BOLD Signal im rechten IC mit der Erregung der Patienten, erfasst über den Hautleitwiderstand (r = -0, 43, p = 0, 05) (siehe Abbildung 3, Seite 8, **Publikation B**).

6.3.3 Fazit

Sowohl die Patientinnen mit BPS als auch die gesunden Kontrollprobandinnen aktivierten in beiden Empathiebedingungen ähnliche Netzwerke. Unter kognitiver Empathie ähnelte dieses Aktivierungsmuster bisher in Studien zu Mentalising, ToM oder Perspektivenübernahme diskutierten Netzwerken (siehe Kapitel 6.1). Das Aktivierungsmuster bezog den Temporal Pol, den STS und den superior frontalen Gyrus (für einen Überblick siehe Frith & Frith, 2005) mit ein. Auch in der emotionalen Empathiebedingung waren Regionen zu identifizieren, die mit Studien zu emotionaler Empathie übereinstimmen, wie z.B. bilateral der IC und der mPFC (Singer & Lamm, 2009).

Im Vergleich der beiden Untersuchungsgruppen, Patientinnen mit BPS und gesunde Kontrollprobandinnen, war ein einziges Cluster unter der kognitiven Empathie bei den Kontrollpersonen aktiver als bei den Patienten mit BPS. Es gab keine Region, bei der die Patienten mit BPS eine höhere Aktivität zeigten als die Kontrollpersonen. Identifiziert wurde eine Ansammlung von Voxeln im linken posterioren STS. Der STS scheint eine wesentliche Rolle in sozial kognitiven Prozessen zu spielen (Saxe & Kanwisher, 2003).

Eine Erklärungsmöglichkeit für diese niedrige Aktivierung im STS bei BPS kommt aus der Bindungsforschung. Studien zum Bindungsverhalten bei Patienten mit BPS erlauben die Schlussfolgerung, dass Misshandlungen in der Kindheit zu eingeschränkten Fähigkeiten der kognitiven Empathie („mentalizing“) der Opfer führen (Fonagy et al., 1996). Diese eingeschränkte Fähigkeit zum Mentalisieren könnte in einer verminderten Aktivität im STS widergespiegelt werden. Frühkindliche Misshandlung (z.B. emotionale Misshandlung, sexueller Missbrauch) durch eine Bezugsperson ist eines der wesentlichen psychosozialen Risiken und prognostischen Faktoren für die BPS Symptomatik (Zanarini et al., 2006). Es könnte auch eine Ursache dafür sein, dass eine Vielzahl von Patienten mit BPS gleichzeitig die Diagnose PTBS bekommen (McGlashan et al., 2000) (siehe Kapitel 5.1). Diese Hypothese wird dadurch gestützt, dass die Patienten, die besonders wenig Aktivierung im STS unter kognitiver Empathie zeigen, von besonders starkem Wiedererleben traumatischer Erinnerungen berichten. Frühkindliche Misshandlungen beeinflussen höchst wahrscheinlich die Entwicklung des Gehirns (Bremner & Vermetten, 2001). Die Entwicklung des STS wird verhältnismäßig spät in der Ontogenese abgeschlossen (Paus, 2005). Damit könnte diese Region auch besonders empfindlich für andauernde psychologische Stressoren in der frühen Kindheit sein.

Unter der emotionalen Empathiebedingung war ein Cluster in der rechten mittleren Insula bei den BPS Patientinnen stärker aktiviert als bei den Kontrollpersonen. Dieser mittlere Bereich des insulären Kortex wurde bisher nicht bei emotionaler Empathie (Singer et al., 2009) sondern bei körperlichem Arousal diskutiert (Brendel et al., 2005). Für emotionale Empathie, vor allem bei Empathie für Schmerz, kam bisher ein eher anteriorer Teil der Insula in Betracht (Singer et al., 2009). Für den

mittleren insulären Bereich wurde eine positive Assoziation zwischen der BOLD Antwort und dem Hautleitwiderstand bei der Patientengruppe gefunden. Diese Korrelation weist auf ein erhöhtes Arousal bei Patienten mit BPS unter emotionaler Empathie hin.

Da emotionale Empathie eine auf eine andere Person gerichtete, angemessen emotionale Reaktion verlangt, kann man emotionale Empathie teilweise auch als einen emotionsregulatorischen Prozess in zwischenmenschlicher Interaktion betrachten. Schwierigkeiten mit Emotionsregulation von Patienten mit BPS (Putnam & Silk, 2005) könnte sich in erhöhtem Arousal und erhöhtem „personal distress" widerspiegeln. Tatsächlich wurde gezeigt, dass das Erfahren von „personal distress" auf das Leiden anderer mit der Aktivierung des mittleren insulären Kortex bei gesunden Kontrollpersonen assoziiert wird (Decety & Moriguchi, 2007). Außerdem wurde hier eine erhöhte Ausprägung von „personal distress" (erfasst über den IRI siehe Kapitel 3.2.3; Davis, 1983) bei Patientinnen mit BPS gefunden. Dies wurde außerdem bereits von Patienten mit BPS berichtet (Guttman & Laporte, 2000). Möglicherweise ist eine erhöhte Ausprägung von „personal distress" eine der Ursachen für reduzierte emotional empathische Fähigkeiten bei den Patienten mit BPS.

Die zweite Region, die eine erhöhte Aktivierung unter emotionaler Empathie bei den Patienten mit BPS verglichen mit den gesunden Kontrollpersonen aufwies, war der rechte anteriore STS. Der rechte STS wurde bereits als sensitiv für die Wahrnehmung der Übereinstimmung zwischen Handlung und Emotionsausdruck beschrieben (Wyk, Hudac, Carter, Sobel & Pelphrey, 2009). Eine erhöhte Aktivierung in dieser Region bei Patienten mit BPS während emotionaler Empathie könnte ein generelles Misstrauen in die emotionalen Reaktionen anderer repräsentieren. Diese Vermutung geht mit Untersuchungen zu Vertrauen und Kooperation bei Patienten mit BPS einher (King-Casas et al., 2008; Unoka, Seres, Aspan, Bodi & Keri, 2009). Gleichzeitig unterstützt sie die These, dass Patienten mit BPS Probleme haben, Emotionen anderer richtig zu interpretieren, wenn sie selbst emotional erregt sind (Wolff, Stiglmayr, Bretz, Lammers & Auckenthaler, 2007).

6.3.4 Untersuchung neuronaler Korrelate von Empathie bei Borderline Patienten mit und ohne komorbid auftretender Posttraumatischer Belastungsstörung

Manuskript A

Auf der Verhaltensebene konnte gezeigt werden, dass eine zusätzlich auftretende PTBS einen verschlechternden Einfluss auf die kognitiv empathischen Fähigkeiten von Patienten mit BPS hat (siehe Kapitel 5.1; **Publikation A,** Preißler et al., 2010). Anschließend wurde mit funktioneller Bildgebung demonstriert, dass während kognitiver Empathie Patientinnen mit BPS erhöhte Aktivierungen im linken STS aufweisen. Der Sauerstoffverbrauch in dieser Region korrelierte in kognitiver Empathie negativ mit der Stärke der berichteten intrusiven Symptomatik (siehe

Kapitel 6.3.2; **Studie 2 aus Publikation B,** Dziobek et al., 2011). Diese beiden Ergebnisse werfen die Frage nach spezifischen Unterschieden von BPS Patienten mit zusätzlicher PTBS und ohne diese Komorbidität auf.

Um diesem Punkt nachzugehen, wurde die in **Studie 2 aus Publikation B** (Dziobek et al., 2011) beschriebene Patientenstichprobe für **Manuskript A** geteilt. Von den 30 BPS Patientinnen hatten 15 eine zusätzliche PTBS und 15 nicht. Unter kognitiver Empathie konnten zwei Regionen identifiziert werden, in denen die Patientinnen ohne komorbide PTBS einen höheren Sauerstoffverbrauch hatten als Patientinnen mit einer zusätzlich auftretenden PTBS, zum einen eine Region im linken OFC (MNI Koordinaten: -30, 36, -8; Clustergröße: 1392), zum anderen im linken Hippocampus (MNI Koordinaten: -16, -32, -10; Clustergröße: 624) (siehe Abbildung 1, **Manuskript A**).

Um die Spezifität dieses Ergebnisses für kognitive Empathie zu überprüfen, wurden diese Regionen als ROI definiert. Anschließend wurde der Sauerstoffverbrauch unter emotionaler Empathie sowie unter der HLB Bedingung (siehe Kapitel 6.3.1) in diesen ROIs betrachtet (siehe Abbildung 1, **Manuskript A**). Auch unter diesen zwei Bedingungen zeigt sich ein ähnliches Muster, wie das für kognitive Empathie beschriebene. Obwohl diese Unterschiede bei dem gewählten Signifikanzniveau in FSL nicht bedeutsam werden, spricht dieses Ergebnis gegen eine Spezifität des Ergebnisses für kognitive Empathie.

Eine Erklärungsmöglichkeit für dieses Ergebnis ist, betrachtet man **Publikation A** (siehe Kapitel 5.1; Preißler et al., 2010) näher, dass Patienten mit einer zusätzlich auftretenden PTBS in kognitiver Empathie eher Einschränkungen im Erkennen von Gedanken und Absichten aufweisen. Im Gegensatz zum Erkennen von Emotionen könnte man das Erkennen von Absichten und Gedanken als Integrationsaufgabe höherer Ordnung betrachten. Das hier verwendete Untersuchungsinstrument (siehe Kapitel 6.3.1) scheint allerdings eher basale kognitiv empathische Fähigkeiten zu erfassen. Bei der näheren Betrachtung von BPS Patienten mit PTBS und ohne PTBS scheint sich hier ein instruktionsunabhängiges, wenn auch bei kognitiver Empathie stärker ausgeprägtes, Muster zu zeigen. Dieses Ergebnis geht mit einem Modell zur PTBS von Rauch und Mitarbeitern einher (Rauch, Shin & Phelps, 2006). Patienten mit PTBS scheinen eine geringere Erregbarkeit, sowohl orbitofrontaler Regionen als auch des Hippocampus zu zeigen.

6.3.5 Fazit

Auf Grund der hier beschriebenen Ergebnisse kann man davon ausgehen, dass BPS Patienten mit einer zusätzlich auftretenden PTBS eine klinische Subgruppe bilden. Diese Patienten haben größere Probleme in kognitiver Empathie als Patienten ohne PTBS. Neben diesem Ergebnis auf Verhaltensebene fand sich für Patienten mit PTBS kein spezifisches neuronales Korrelat für ihre

Einschränkungen in kognitiver Empathie. Allerdings lassen sich BPS Patienten mit PTBS auch durch ein spezielles Muster an Reaktionen auf emotionale Stimuli im Allgemeinen von Patienten mit BPS und ohne PTBS unterscheiden. Die hier dargestellten Befunde sprechen für eine gestörte Aktivität in der Verbindung zwischen OFC und Hippocampus bei BPS Patienten mit PTBS (Bremner et al., 2003; Rauch et al., 2006). BPS Patienten mit einer zusätzlichen PTBS Diagnose sollten in der Forschung und in der Therapie besonders berücksichtigt werden.

6.4 Strukturelle neuroanatomische Untersuchung

Wie bereits dargestellt (Kapitel 6.2.3) gibt es unterschiedliche Befunde zu strukturellen Veränderungen bei BPS. Auch hier scheint die Rolle des Einflusses einer komorbiden PTBS bisher wenig Berücksichtigung gefunden zu haben. Daher werden in **Manuskript B** Patienten ohne komorbide PTBS betrachtet. Es sollen die strukturellen Abweichungen aufgezeigt werden, die spezifisch für BPS sind.

Es ist auffällig, dass sich bisherige Studien zu morphologischen Veränderungen bei Patienten mit BPS nur auf das Volumen von sowohl grauer als auch weißer Substanz beziehen (Kapitel 6.2.3). Das Subtanzvolumen stellt lediglich eine grobe Abbildung von quantitativen kortikalen Veränderungen dar. Die Berechnung des grauen Substanzvolumens setzt sich zusammen aus der Oberfläche der jeweiligen Gehirnregion und ihrer kortikalen Dicke. Damit könnten Veränderungen in nur einem Parameter, wie kortikaler Dicke, übersehen werden (Fornito et al., 2008). Aufgrund technischer Neuentwicklungen ist es möglich, einzelne Veränderungen in unterschiedlichen Parameter und nicht nur im Volumen zu betrachten (Fischl & Dale, 2000). Insbesondere die Messung kortikaler Dicke scheint für Studien mit psychiatrischen Patienten von besonderer Relevanz zu sein (Fjell et al., 2006; Shaw et al., 2006). Da die Betrachtung kortikaler Dicke demnach mehr Informationen bezüglich der zugrundeliegenden Pathologie liefern kann, wird in **Manuskript B** (siehe Kapitel 6.4) dieses Maß verwendet, um den Einfluss der BPS Symptomatik unabhängig vom Einfluss einer komorbid auftretenden PTBS auf die Struktur des Gehirns näher zu untersuchen.

Manuskript B

In die MRT-Untersuchung (**Manuskript B**) konnten die Daten von 31 Patientinnen mit BPS und 27 gesunder Kontrollprobandinnen eingeschlossen werden. Vierzehn der Patientinnen hatten eine zusätzlich auftretende PTBS. Die Datenvorverarbeitung und Analyse erfolgte mit FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). In den Analysen wurde kortikale Dicke als Maß für anatomische Eigenschaften verwendet. Kortikale Dicke hat sich als ähnlich sensitiv wie manuelle

Segmentierung herausgestellt (Morey et al., 2009) und ist gleichzeitig sensitiver für minimale Veränderungen als voxel-basierte Morphometrie (Bookstein, 2001).

Nach den FreeSurfer internen Auswertungsschritten (siehe **Manuskript B**) wurden zuerst gesunde Kontrollpersonen mit allen Patienten mit BPS verglichen. In diesem Kontrast konnte nur ein Cluster (Vertexanzahl: 861 mm^3) im rostralmiddlefrontalen Kortex der rechten Hemisphäre identifiziert werden. In diesem weisen die Patienten mit BPS eine größere regionale kortikale Dicke als die gesunden Kontrollprobandinnen auf (Talairach-Koordinaten des Peak Vertex: 18,4; 56,3; -14,7). Anschließend wurden die Analysen auf Patienten beschränkt, die keine zusätzliche PTBS haben. Hier wurde ein Cluster identifiziert, das im Wesentlichen mit dem Cluster aus dem eben beschriebenen Kontrast übereinstimmt. Das Cluster liegt demnach auch im rechten rostralmiddlefrontalen Kortex (Vertexanzahl: 856 mm^3; Talairach-Koordinaten des Peak Vertex: 18,8; 56,8; -14,3). In beiden Kontrasten konnte für die linke Hemisphäre kein Cluster identifiziert werden. Für alle weiteren möglichen Gruppenunterschiede wurde keine Region mit signifikant unterschiedlicher kortikaler Dicke gefunden.

Fazit:

In dieser Untersuchung wurden erstmalig Unterschiede in kortikaler Dicke bei Patienten mit BPS im Vergleich zu gesunden Kontrollpersonen festgestellt. Dieser Unterschied bleibt erhalten, wenn man die Gruppe um BPS Patienten mit einer zusätzlichen PTBS bereinigt. Die Zunahme an kortikaler Dicke im rostralmiddlefrontalen Kortex, einer Subregion des DLPFC, scheint demnach BPS spezifisch und nicht PTBS bedingt zu sein.

7. Zusammenfassende Diskussion

Mit der vorliegenden Arbeit werden drei Publikationen und zwei Manuskripte eingereicht. In diesen Arbeiten sind fünf empirische Studien dargestellt. Die Untersuchungen wurden in den vorangegangen Abschnitten beschrieben und in den bisherigen Stand der Forschung eingeordnet. Zusammenfassend konnten folgende Befunde gezeigt werden:

- Patientinnen mit BPS weisen Defizite in sowohl kognitiver als auch emotionaler Empathie auf.
- Defizite in kognitiver Empathie werden durch eine komorbide Achse I Störung (PTBS) verstärkt.
- Im Gegensatz zu dem verstärkenden Einfluss einer komorbiden PTBS hat eine NPS keinen Einfluss auf kognitiv empathische Fähigkeiten, sondern betrifft emotionale Empathie.

- Man kann das „empathische Muster“ von Patienten mit BPS von dem der Patienten mit NPS abgrenzen.
- Patientinnen mit BPS rekrutieren unter kognitiver und emotionaler Empathie die unter Empathiebedingungen klassisch diskutierten Netzwerke.
- BPS Patientinnen zeigen unter kognitiver Empathie weniger Aktivität im linken STS. Dies ist mit der Stärke ihrer intrusiven Symptomatik assoziiert.
- Unter emotionaler Empathie ist ein Cluster in der rechten mittleren Insula bei den Patientinnen stärker als bei den Kontrollpersonen aktiviert. Diese insuläre Region ist eher für körperliche Erregung als für emotionale Empathie bekannt. Es wird vermutet, dass die Probleme der Patienten in Emotionsregulation über ein erhöhtes Arousal und starken „personal distress“ Probleme in emotionaler Empathie vermitteln.

BPS Patienten mit einer komorbiden PTBS rekrutieren den linken OFC und linken Hippocampus bei der Konfrontation mit emotionalen Gesichtern weniger als BPS Patienten ohne komorbide PTBS.
Patienten mit BPS weisen eine Zunahme in kortikaler Dicke im DLPFC auf.

Für die ausführliche Diskussion der einzelnen Untersuchungsergebnisse wird hier auf die entsprechenden Publikationen und Manuskripte verwiesen.

7.1 Borderline Empathie

Aus der klinischen Beobachtung ist für BPS das Konzept der „Borderline Empathie” beschrieben. In der folgenden Diskussion sollen die bisher dargelegten Ergebnisse im Rahmen der „Borderline Empathie“ abschließend betrachtet werden.
„Borderline Empathie“ bezeichnet eine besondere Sensitivität für die Umgebung und auch für subtile Änderungen in der Stimmung und im Verhalten bei Patienten mit BPS (Krohn, 1974). Das Konzept entstand auf Basis klinischer Beobachtungen und postuliert bessere Fähigkeiten von BPS Patienten, vor allem in empathischen Prozessen (Krohn, 1974). Es steht in starkem Kontrast zu den von BPS Patienten berichteten Probleme in zwischenmenschlichen Beziehungen (Modestin, 1987; Zanarini, Gunderson, Frankenburg & Chauncey, 1990). Außerdem werden gerade derartige Probleme als eines der Hauptmerkmale von BPS betrachtet (Gunderson, 2007).
Die Ergebnisse in den hier vorgestellten Studien widersprechen dem Konzept der „Borderline Empathie“. Sie gehen einher mit den, von BPS Patienten berichteten Problemen im zwischenmenschlichen Bereich und bieten eine mögliche Erklärung für diese. Patienten mit BPS zeigten in den hier präsentierten Verhaltensstudien Einschränkungen sowohl in kognitiver als auch emotionaler Empathie. Daher sprechen die hier dargestellten Daten nicht dafür, dass Patienten mit

BPS besser das Verhalten anderer voraussagen können. Neben den hier präsentierten Studien ist festzuhalten, dass in den letzten Jahren ein starkes Interesse an der zwischenmenschlichen Problematik bei BPS aufgetreten ist. Daher sind Ergebnisse anderer Forschungsgruppen zu erwähnen, die sich auch mit „Borderline Empathie“ auseinandersetzen. Die hier vorgestellten Daten stehen im Widerspruch zu den Ergebnissen dieser Arbeitsgruppen (Arntz et al., 2009; Fertuck et al., 2009). Die Arbeitsgruppe um Fertuck (2009) verwendete den RME (siehe Kapitel 3.2.1; Baron-Cohen et al., 2001). Sie stellten bei BPS Patienten bessere sozial-kognitive Fähigkeiten im Vergleich zu gesunden Kontrollpersonen fest. In der hier dargestellten Verhaltensstudie (siehe Kapitel 4.2; **Publikation A,** Preißler et al., 2010) konnte der RME keine Unterschiede zwischen gesunden Kontrollpersonen und Patienten mit BPS aufzeigen. Eine mögliche Ursache für diesen Unterschied ist die Stichprobenzusammensetzung. Zum Einen waren in der Studie von Fertuck et al. (2009) wesentlich mehr Männer eingeschlossen als in **Publikation A** (Preißler et al., 2010). Männer sind weniger exakt und weniger sensibel bei der Zuschreibung menschlicher Emotionen in Gesichtern (Montagne, Kessels, Frigerio, de Haan & Perrett, 2005). Auch bei einem Blick auf die Performanz der Kontrollpersonen lässt sich anmerken, dass in der Stichprobe von Fertuck et al. (2009) diese, verglichen mit anderen Studien, die den RME einsetzten, am unteren Ende der Spannweite des Antwortspektrums lagen. Ein dritter möglicher Grund ist, dass der RME hauptsächlich Augenregionen kaukasischer Personen darstellt und die gesunde Kontrollgruppe bei Fertuck et al. (2009) einen großen Prozentsatz nicht kaukasischer Teilnehmer enthält. Diese drei Punkte zusammengenommen bieten eine mögliche Erklärung, warum sich die Ergebnisse der Studie von Fertuck et al. (2009) von den Ergebnissen der hier präsentierten Studien unterscheiden.

Auch die Untersuchungsergebnisse von Arntz und Mitarbeitern (2009) stehen im Gegensatz zu den hier dargestellten Verhaltensdaten. Sie untersuchten kognitive Empathie oder ToM mit einer Kurzgeschichtenaufgabe von Happé (1994). Die Autoren verglichen die ToM Leistung von BPS Patienten mit Patienten einer Cluster C Persönlichkeitsstörung sowie mit gesunden Kontrollpersonen. Die Patienten mit BPS unterschieden sich von keiner der beiden Vergleichsgruppen (Arntz et al., 2009). Möglicherweise liegt der Unterschied zu den hier dargestellten Ergebnissen an der Testauswahl. In den hier vorgestellten Arbeiten wurden komplexere und ökologisch validere Testverfahren (MASC in **Publikation A und C**; MET in **Publikation B und C**) verwendet und nur mit diesen konnte ein Unterschied zwischen Patienten mit BPS und gesunden Kontrollprobanden nachgewiesen werden.

Die beide gerade dargestellten Studien gehen demnach mit Vermutungen zur „Borderline Empathie“ einher (Arntz et al., 2009; Fertuck et al., 2009). Die hier beschriebenen Befunde stehen im Widerspruch zu diesem Konzept. Sie gehen aber einher mit der Theorie von Fonagy und Bateman (2008). Diese Autoren entwickelten eine spezifische Therapierichtung, die u.a. auf die Verbesserung

der empathischen Fähigkeiten abzielt. Sie ist nachgewiesen effektiv für BPS (Fonagy & Bateman, 2008). Allerdings fehlte dieser Therapierichtung eine empirische Fundierung, welche durch die hier dargelegten Befunde gegeben wird.

Außerdem hat die Arbeitsgruppe um Fonagy und Bateman in einer gerade publizierten Studie (Sharp et al., 2011) Jugendliche mit BPS-Ausprägungen mit dem MASC (siehe Kapitel 3.2.2; Dziobek et al., 2006) untersucht. Ihre Ergebnisse gehen in die gleiche Richtung, wie die hier dargestellten Verhaltensdaten und kombinieren diese mit Problemen in der Emotionsregulation. Schwierigkeiten mit der Emotionsregulation werden bei Patienten mit BPS schon seit langem diskutiert (Glenn & Klonsky, 2009; Putnam & Silk, 2005).

Beide Konzepte, fehlerhafte Emotionsregulation und Probleme in Empathie, scheinen demnach miteinander verknüpft zu sein. Dies konnte in den hier dargestellten Studien auch präsentiert werden. Die neuronalen Aktivierungen unter der emotionalen Empathiebedingung scheinen durch emotionsregulatorische Probleme der Patienten mit BPS bedingt zu sein. Eine mögliche Ursache dafür kann man bereits in der Definition von emotionaler Empathie als „angemessene emotionale Reaktion einer anderen Person gegenüber“ (Davis, 1994) sehen. Diese Definition verweist bereits durch die Begrifflichkeit „angemessen“ darauf, dass Emotionsregulation nötig ist, um emotional empathisch zu reagieren. Damit könnte man emotionale Empathie als einen emotionsregulatorischen Prozess in interpersonellen Situationen betrachten.

Aus den hier dargestellten Daten lässt sich vermuten, dass der Zusammenhang zwischen emotionaler Empathie und emotionsregulatorischen Prozessen der einer umgekehrt U-förmigen Funktion ist und über die Aktivität der mittleren Insula vermittelt wird. Des Weiteren scheinen auch spezielle strukturelle Veränderungen mit den emotionsregulatorischen Defiziten der BPS Patienten einherzugehen.

Die hier gefunden funktionellen Unterschiede bei emotionaler und kognitiver Empathie stehen wie die Verhaltensdaten im Widerspruch zu Konzepten unveränderter oder gar verbesserter Empathiefähigkeit bei BPS Patienten. Auf Basis der hier beschrieben Daten kann man davon ausgehen, dass das Konzept der „Borderline Empathie“ nicht durch besondere empathische Fähigkeiten von BPS Patienten entstanden ist. Vielmehr lässt sich vermuten, dass es durch Unvorhersehbarkeit der Reaktion der Patienten bedingt wurde (Flury, Ickes & Schweinle, 2008; King-Casas et al., 2008).

7.2 Fazit und Ausblick

Die Probleme in Empathie könnten ermöglichen, die dysfunktionalen Beziehungen von Patienten mit BPS zu verstehen. Die hier dargelegten Untersuchungen zeigen, dass Patienten mit BPS Probleme in beiden Facetten von Empathie aufweisen. Diese Defizite sind begleitet von Veränderungen in der neuronalen Aktivität. Untersuchungen aus der Bindungsforschung und die hier dargelegten Daten weisen daraufhin, dass diese Probleme u.a. durch frühkindliche Misshandlungen verursacht bzw. verstärkt sein könnten. Um dies weiter abklären zu können, sind Studien nötig, die das Bindungsverhalten von Patienten mit BPS, z.B. mit dem „Adult Attachement Interview“, näher untersuchen und diese Ergebnisse in Zusammenhang mit den empathischen Fähigkeiten der untersuchten Patienten bringen.

Es konnte in den dargestellten Untersuchungen wiederholt gezeigt werden, dass Patienten mit einer komorbid auftretenden PTBS eine diagnostische Subgruppe bilden, die in der Therapie eine besondere Beachtung finden sollte, da diese Patienten anscheinend insbesondere in ihrer kognitiven Empathie stark eingeschränkt sind. Zukünftige Studien sollten hier vor allem bei der Untersuchung neuronaler Korrelate stärker auf kognitive Empathie fokussieren.

So sollten gerade BPS Patienten mit einer komorbiden PTBS von einer Therapie wie „mentalization based therapy“ nach Fonagy und Bateman (2008) profitieren, die auf die Verbesserung ihrer sozial kognitiven Fähigkeiten abzielt. Der Erfolg von unterschiedlichen Therapierichtungen, wie Dialektisch-Behaviorale Therapie, Transference-Focused Psychotherapie, schemazentrierte Therapie, “mentalization based therapy“ oder unterstützende Psychotherapie (für einen Überblick siehe de Groot, Verheul & Trijsburg, 2008) auf emotionaler und kognitiver Empathiefähigkeiten der Patienten mit BPS sollte mit Längsschnittstudien überprüft werden.

Die hier dargelegten Ergebnisse lassen allerdings hoffen, dass eine Therapie, die auf die Verbesserung dieser Fähigkeiten abzielt, bei Patienten mit BPS auch die zwischenmenschlichen Beziehungen verbessert und damit den Leidensdruck der Patienten lindert.

8. Abbildungsverzeichnis

9. Abkürzungsverzeichnis

α	Cronbach's Alpha
ACC	anterior cingulärer Kortex
BOLD	blood oxygenation level dependent
BPS	Borderline-Persönlichkeitsstörung
BSL	Borderline-Symptom-List
DSM IV-TR	Diagnostisches und Statistisches Manual psychischer Störungen – Textrevision
fMRT	funktionelle Magnet-Resonanz-Tomographie
IAPS	International Affective Picture System
IC	insulärer Kortex
IRI	Interpersonal Reactivity Index
MASC	Movie for the Assessment of Social Cognition
MET	Multifaceted Empathy Test
METcore	Multifaceted Empathy Test considered and revised
mPFC	medial-präfrontaler Kortex
MRT	Magnet-Resonanz-Tomographie
NPS	Narzisstische Persönlichkeitsstörung
OFC	orbitofrontaler Kortex
PDS	Posttraumatische Diagnose Skala
PFC	präfrontaler Kortex
PTBS	Posttraumatische Belastungsstörung
REM	Reading the Mind in the Eyes Test
ROI	region of interest
ToM	Theory of Mind
TPJ	temporo-parietale Junction
STS	superior temporaler Sulcus

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11. Anhang

Veröffentlichungen und Manuskripte

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Preißler, S., Dziobek, I., Ritter, K., Heekeren, H. R., & Roepke, S. (2010). Social Cognition in Borderline Personality Disorder: Evidence for Disturbed Recognition of the Emotions, Thoughts, and Intentions of Others. *Front. Behav. Neurosci, 4: 182.*

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Social cognition in borderline personality disorder: evidence for disturbed recognition of the emotions, thoughts, and intentions of others

Sandra Preißler[1], Isabel Dziobek[2,3], Kathrin Ritter[1], Hauke R. Heekeren[2,3] and Stefan Roepke[1,3]**

[1] Department of Psychiatry, Campus Benjamin Franklin, Charité – University Medicine Berlin, Berlin, Germany
[2] Max-Planck-Institute for Human Development, Neurocognition of Decision Making Group, Berlin, Germany
[3] Cluster of Excellence Languages of Emotion, Freie Universität Berlin, Berlin, Germany

Edited by:
Dominique J. F. de Quervain, University of Basel, Switzerland

Reviewed by:
Jenifer Bartz, Mount Sinai School of Medicine, USA
Arnoud Arntz, University of Maastrich, Netherlands

***Correspondence:**
Sandra Preißler and Stefan Roepke, Department of Psychiatry, Campus Benjamin Franklin, Charité – Universitätsmedizin Berlin, Eschenallee 3, D-14050 Berlin, Germany.
e-mail: preissler.sandra@googlemail.com; stefan.roepke@charite.de

Disturbed relatedness is a core feature of borderline personality disorder (BPD), and impaired social cognition or deficits in "mentalization" are hypothesized to underlie this feature. To date, only weak empirical evidence argues for impairment in the recognition of emotions, thoughts, or intentions in BPD. Data from facial emotion recognition research indicate that these abilities are altered in BPD only if tasks are complex. The present study aims to assess social cognitive abilities in BPD. Sixty-four women with BPD and 38 healthy controls watched the "Movie for the Assessment of Social Cognition" (MASC), a newly developed film displaying social interactions, and asking for an assessment of the intentions, emotions, and thoughts of the characters. In addition, participants completed an established but less ecologically valid measure of social cognition ("Reading the Mind in the Eyes"; RME). In the RME task, BPD patients did not display impairment in social cognition compared to healthy controls. By contrast, on the more sensitive MASC, women with BPD showed significantly impaired abilities in social cognition compared to healthy controls in their recognition of emotions, thoughts, and intentions. Comorbid PTSD, intrusions, and sexual trauma negatively predicted social cognitive abilities on the more sensitive MASC. Thus, our results suggest impaired social cognitive abilities in BPD. Especially for comorbid PTSD, intrusive symptoms, and history of sexual trauma predicted poor outcomes on social cognition tasks.

Keywords: borderline personality disorder, MASC, PTSD, empathy, social cognition, theory of mind, mentalization, trauma

INTRODUCTION

Borderline personality disorder (BPD) is a severe mental disorder, affecting up to 5.9% of the general population (Grant et al., 2008). This disorder heavily impairs affected individuals in multiple domains (Skodol et al., 2005) and presents a major burden to public health systems (Soeteman et al., 2008).

Three symptom clusters have been identified in BPD, namely affective dysregulation, impulsivity (behavioral dysregulation), and disturbed relatedness (Sanislow et al., 2002).

Affective dysregulation and impulsivity have been the focus of empirical studies, and have been identified as phenotypic traits of BPD in longitudinal studies (Zanarini et al., 2005), behavioral experiments (Domes et al., 2009), and brain imaging studies (Domes et al., 2009).

By contrast, disturbed relatedness in BPD has only been analyzed in a limited number of studies to date (e.g., Skodol et al., 2005; Hill et al., 2008; King-Casas et al., 2008), although the relational style of BPD has been suggested to be the best discriminator for diagnosis (Gunderson, 2007).

A major challenge in studying social interaction is the development of empirical tests that are close to real-life conditions (ecologically valid) with consistent underlying theoretical constructs that are capable of capturing major aspects of deviant relatedness as described in BPD.

A study by Frank and Hoffman (1986) compared BPD patients with clinical controls using a shortened version of the profile of non-verbal sensitivity (PONS; DePaulo and Rosenthal, 1979), in which participants had to choose one of two alternative affective descriptions after watching a 10-min video containing depictions of different emotional situations, each portrayed by the same woman. Borderline patients scored higher than controls on this measure of non-verbal sensitivity. Ladisich and Feil (1988) measured how well a member of an interacting group could predict the self-rated feelings of the other group members. BPD patients achieved the highest scores compared to other patients; they actually achieved scores comparable to the participating psychiatrist. These early findings and clinical observations (Krohn, 1974; Carter and Rinsley, 1977) led to the descriptive term "borderline empathy."

On the other hand, research with projective material from the Thematic Apperception Test and other narratives (Westen, 1990, 1991a,b; Westen et al., 1990a,b,c,d; Nigg et al., 1992; Segal et al., 1992, 1993) has indicated that BPD patients are able to make complex intentional attributions of other people's actions although they express more malevolent representations of others compared to controls (Veen and Arntz, 2000). A study by Arntz and Veen (2001) even found evidence for less complexity in BPD patients' character descriptions after watching film sequences of emotional and non-emotional film sequences.

Recent advances in conceptualizing (Frith and Frith, 2005) and measuring social cognition could provide the possibility for empirically assessing the basic principles of the clinically observed disturbed relatedness in BPD (Hill et al., 2008). The concept of social cognition highly overlaps with the constructs of "theory of mind" (Premack et al., 1978) and "mentalizing" (Frith and Frith, 2006), and describes the ability to infer another's thoughts, feelings, and intentions.

Fonagy et al. (1996) provided preliminary evidence that impaired social cognition, as assessed by the Adult Attachment Interview (de Haas et al., 1994), is linked to BPD symptomatology. Also, Harari et al. (2010) found cognitive empathy, assessed with the interpersonal reactivity index (IRI; Davis, 1983), and "theory of mind," assessed with the "Faux pas" task (Baron-Cohen et al., 1997), to be impaired in BPD patients compared to controls. Nevertheless, these results are not consistent, as Arntz et al. (2009) could not find a deficit in "theory of mind" capacities in BPD patients, assessed with the advanced "theory of mind" task (Happé, 1994). Whereas Fertuck et al. (2009) found even enhanced mental state discrimination in BPD patients compared to controls with the "Reading the Mind in the Eyes" task (Baron-Cohen et al., 2001). Nevertheless, Fertuck et al.'s (2009) deficits in social cognition are considered core features of the disorder (Fonagy and Bateman, 2008). Furthermore, a specific form of psychotherapy called mentalization-based therapy has been developed and proven effective for BPD treatment (Fonagy and Bateman, 2008).

Most other prior studies on social cognition in BPD have used mainly facial emotion recognition tasks (e.g., by using static images, such as Ekman faces or morphing pictures; Lynch et al., 2006; Domes et al., 2008). The results of these studies have not been entirely consistent; in some studies patients with BPD were able to correctly identify emotional facial expressions, at times even more accurately than healthy controls (Wagner and Linehan, 1999; Lynch et al., 2006). In one study, neutral facial expressions were interpreted more negatively (Wagner and Linehan, 1999). In another study, Domes et al. (2008) examined the ratings of pictures of faces displaying two basic emotions at the same time (i.e., a blend), morphing from one emotion to the other. BPD patients showed a bias toward the perception of anger (Domes et al., 2008).

However, when facial emotion recognition tasks imitate more complex situations [e.g., by setting time limits for recognizing emotions in faces (Dyck et al., 2009), or with additional prosodic information (Minzenberg et al., 2006)], patients with BPD show increased error rates. Thus, these findings indicate that BPD patients show impairments in social cognition only on tasks that are more ecologically valid.

Also, results from facial emotion recognition tasks show that intrusive symptoms and comorbid PTSD are negative predictors for emotion recognition abilities in BPD (Dyck et al., 2009). This finding is of special interest, as many patients with BPD have childhood histories of sexual and/or physical abuse (Zanarini et al., 2002). Furthermore, comorbid PTSD is frequent in this group, and predicts a poor long-term outcome of the disorder (Zanarini et al., 2006). Thus, in addition to high heritability of BPD (Torgersen et al., 2008), these results argue that environmental factors (e.g., trauma) contribute to disturbed social cognition in BPD. In summary, for the current study we expected PTSD to be a negative predictor of social cognition.

As mentioned, empirical studies of social interactions are limited by the use of ecologically valid assessment instruments. These instruments are widely lacking. Our group recently developed the "Movie for the Assessment of Social Cognition" (MASC; Dziobek et al., 2006), which is a film displaying social interactions among multiple characters. The MASC empirically assesses the participant's recognition of the intentions, emotions, and thoughts of the movie characters, and allows for the analysis of social cognition in a more complex and ecologically valid manner.

The aim of the present study was twofold: First, we aimed to assess facets of social cognition in patients with BPD compared to controls, and second, we aimed to evaluate the impact of BPD symptomatology, comorbidity, and history of traumatic events on social cognitive abilities.

MATERIALS AND METHODS

SUBJECTS

Sixty-four women with the diagnosis of BPD according to DSM-IV (American Psychiatric Association, 2000), and 38 healthy, age and IQ matched female comparison subjects participated in the study. All patients were admitted to our inpatient treatment program for BPD at the Department of Psychiatry, Charité – Universitätsmedizin Berlin, Germany, during which they were consecutively recruited into the study. Prior to hospital admission, all of them were on a waiting list and none was admitted for acute care. Patients were not reimbursed for study participation. Healthy controls were recruited via media advertisements and reimbursed for participation. All data were assessed between December, 2006, and June, 2008.

Axis II diagnoses were confirmed or excluded in patients and controls, respectively, with the German version of the Structured Clinical Interview for DSM-IV (SCID II; First et al., 1997), and Axis I diagnoses were assessed with the German version of the Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998). Fluid IQ was assessed with subtest 4 of the "Leistungsprüfsystem" (Horn, 1983), a standard German intelligence test. This test shows high validity and a good reliability (retest reliability = 0.77). On subtest 4, participants have to recognize regularities and irregularities in series of numbers and letters; thus, only minimal education in terms of basic knowledge of numbers and letters is needed. In the standard procedure of the test, as applied in this study, IQ values are adapted for age. The study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin. All participants provided written informed consent after having received a thorough explanation of the study.

Exclusion criteria for the patients consisted of mental retardation, schizophrenia, and age younger than 18 years. Sociodemographic and clinical parameters of patients and controls are presented in **Table 1**. Later, patients were divided into two groups, one with and one without comorbid PTSD. These three groups (controls and two patient groups) were not statistically significantly different in age and fluid IQ (age: controls: mean = 31.66, SD = 10.27; patients with PTSD: mean = 29.36, SD = 8.27; patients without PTSD: mean = 29.05, SD = 9.26; $F(2, 99) = 0.83$, $p = 0.440$; IQ: controls: mean = 120.11, SD = 10.27; patients with PTSD: mean = 115.57, SD = 9.64; patients without PTSD: mean = 117.47, SD = 11.59; $F(2,94) = 1.30$, $p = 0.275$).

Table 1 | Sociodemographic and clinical variables of women with borderline personality disorder and healthy comparison subjects.

	Patients with borderline personality disorder (*N* = 64)		Healthy comparison subjects (*N* = 38)			
	Mean	SD	Mean	SD	*t*	η^2
Age (years)	29.2	8.9	31.7	10.3	−1.29	0.017
Fluid intelligence[a]	116.7	10.9	120.1	10.3	−1.49	0.023
MDE	***N***	**%**				
Lifetime	27	42.2				
Current	8	12.5				
Current dysthymia	22	34.4				
Substance use disorder (last 12 month)	12	18.8				
Any anxiety disorder	37	57.8				
Current PTSD	23	35.9				
Any eating disorder	16	25				
Any cluster A PD	6	9.4				
Any other Cluster B PD	7	10.9				
Any cluster C PD	27	42.2				
No psychotropic medication	43	67.2				
Current medication						
Antidepressants	20	31.2				
Atypical antipsychotics	7	10.9				

PTSD, posttraumatic stress disorder; SD, standard deviation; PD, personality disorder.
[a]*Measured by subtest 4 of the "Leistungsprüfsystem" (Horn, 1983).*

"READING THE MIND IN THE EYES" TASK

The revised version of the "Reading the Mind in the Eyes" task (RME; Baron-Cohen et al., 2001) involves inferring the mental state of a person solely from information conveyed by photographs of that person's eyes. The RME includes 40 items. Participants were asked to pick, for each pair of eyes, one out of four mental state descriptors (e.g., interested, hostile), where the descriptors varied for each item. The test is scored by adding up the number of mental state attributions correctly identified. The RME had an acceptable internal consistency in our dataset (Cronbach's $\alpha = 0.71$).

MOVIE FOR THE ASSESSMENT OF SOCIAL COGNITION

The "Movie for the Assessment of Social Cognition" (MASC; Dziobek et al., 2006) requires subjects to attribute mental states to movie characters in an everyday life-relevant context. The MASC involves watching a 15 min movie about four persons spending an evening together having dinner. Dominant topics in the movie consist of dating and friendship issues. The film is paused at 45 points, and questions concerning the characters' feelings, thoughts, and intentions are asked (e.g., "What is Betty feeling?," "What is Cliff thinking?," "Why is Michael doing this?"). In detail, the MASC considers 15 items demanding the interpretation of emotions, 14 items for intentions, and 4 items for measuring thoughts.

The MASC has high interrater reliability (ICC = 0.99), and high test-retest reliability ($r = 0.97$; Dziobek et al., 2006). In the present sample, the MASC total scale shows high internal consistency (Cronbach's $\alpha = 0.86$). The internal consistency of the MASC subscale is fairly good (MASC emotions: Cronbach's $\alpha = 0.62$; MASC thoughts: Cronbach's $\alpha = 0.55$; MASC intentions: Cronbach's $\alpha = 0.71$). In the original validation study of the task using individuals on the autism spectrum, a population with possibly selective problems in social cognition, high correlations of the MASC score with social functioning have been found (Dziobek et al., 2006). Each correct response is scored as one point and responses are added together to form a total score. In addition, the MASC allows for a separate quantification of the extent to which emotional mental states, thoughts, and intentions are inferred correctly. In our sample, no correlation between the fluid IQ measure and the MASC sum score was found ($r = 0.096$, $p = 0.356$).

BORDERLINE SYMPTOM LIST

The "Borderline Symptom List" (BSL) is a dimensional self-report measure specifically developed to quantify borderline symptomatology (Bohus et al., 2007). The scale achieved high internal consistency (Cronbach's $\alpha = 0.97$ for the sum score), test-retest reliability ($r = 0.84$ for the total scale), and validity (scale intercorrelations ranged from 0.21 to 0.68; Bohus et al., 2007). The BSL-95 contains a list of 95 subjective complaints and impairments often reported by patients with BPD. These BSL items are based on criteria from the DSM-IV (American Psychiatric Association, 2000), the revised version of the Diagnostic Interview for BPD (Gunderson et al., 1981), and the opinions of both clinical experts and patients with BPD. The questionnaire uses a Likert-type rating format (0 = "not at all," 1 = "a little," 2 = "rather," 3 = "much," and 4 = "very strong"), asking the patient to evaluate their symptoms during the past week. Factor analyses revealed seven factors: self-image, affect regulation, auto aggression, dysthymia, social isolation, intrusions, and hostility. The "intrusions" subscale of the BSL reflects PTSD symptomatology and entails items such as: "I could hardly control my memories," "I was tortured by images," and "I suffered from nightmares." A total score and subscores for the seven factors can be computed.

POSTTRAUMATIC STRESS DIAGNOSTIC SCALE

To measure traumatic experiences as well as to indicate the severity of the comorbid posttraumatic stress disorder, we used the "Posttraumatic Stress Diagnostic Scale" (PDS; Foa, 1995). The PDS is a self-report measure in which the patient is asked to indicate which of a list of traumatic experiences she or he or somebody else underwent in the past. The questionnaire is designed to aid in the detection and diagnosis of PTSD. It parallels DSM-IV (American Psychiatric Association, 2000) diagnostic criteria for a PTSD diagnosis.

STATISTICAL ANALYSIS

For sufficient power (80%) of the study, a sample size of $n = 968$ would be required to detect small effect sizes ($f = 0.10$). For large effect sizes ($f = 0.40$), a sample size of 64 would be needed, and for medium effect sizes ($f = 0.25$), a sample size of 158 would

be necessary (Erdfelder et al., 1996). All further analyses were conducted with SPSS, version 15.0 (SPSS, Chicago). Before use of parametric tests, histograms and Kolmogorov–Smirnov tests were performed to demonstrate normality of variable distributions. Between-groups comparisons were done with univariate analysis of variance (ANOVA). Further analysis was performed with multiple analyses of variance (MANOVA). In an exploratory analysis, IQ was added as a covariate in an ANCOVA model for the two (patients with BPD and healthy controls) and the three groups (BPD patients with PTSD, BPD patients without PTSD, and healthy controls), which revealed no significant influence of IQ for either analysis ($p > 0.50$) and thus, this covariate was excluded from the analyses. Furthermore, we carried out a multiple stepwise regression analysis to derive the best multivariate equation between a dependent (e.g., measure for social cognition) and multiple independent parameters (e.g., comorbidity, psychopathological symptoms, history of trauma). All significance levels were set to 0.05 (two tailed). All values are given as means and standard deviations (SD) when appropriate.

RESULTS

SOCIAL COGNITION IN BPD

To assess differences between patients with BPD and controls in RME, we performed an ANOVA ($F(1, 93) = 0.30$, $p = 0.588$), which did not reveal any group differences (**Table 2**).

Further, differences between patients with BPD and healthy controls on the MASC were calculated with an ANOVA model for the MASC total score ($F(1, 102) = 17.56$, $p < 0.001$). The analysis revealed significantly lower scores for patients with BPD (**Table 2**).

Table 2 | Group comparison between patients with borderline personality disorder and controls in the "Reading the Mind in the Eyes" test and the "Movie for the Assessment of Social Cognition" (MASC).

	Patients with borderline personality disorder ($N = 64$)		Healthy comparison subjects ($N = 38$)			
	Mean	SD	Mean	SD	F^a	η^2
"Reading the mind in the eyes" sum score	24.3	5.6	24.9	3.5	0.30	0.00
MASC sum score	29.9	7.8	35.6	3.9	17.6**	0.15
MASC subscore emotion	10.5	3.2	11.8	1.7	5.5*	0.05
MASC subscore thoughts	3.1	0.9	3.5	0.6	6.1*	0.05
MASC subscore intentions	8.9	2.8	11.0	1.9	16.6**	0.14

SD, standard deviation.
*[a]ANOVA model for "Reading the mind in the eyes" comparison, ANOVA model for "MASC sum score" and MANOVA model for "MASC subscores," *$p < 0.05$, **$p < 0.01$.*

For MASC subscore analyses, the MANOVA revealed significant differences between groups, Wilks-Lambda, $F(3, 102) = 5.78$, $p = 0.001$. All MASC subscores were significantly lower for the BPD group, indicating significant impairments in inferring the emotions, thoughts, and intentions of other persons (**Table 2**).

COMORBID PTSD AND INTRUSIVE SYMPTOMS

To elucidate whether specific symptoms of BPD account for the deficits on the MASC scales, in a first step and for preliminary exploratory data analysis, four stepwise forward linear regression analyses within the BPD group were performed. The seven BSL subscales served as independent variables to predict the MASC total score or subscales. A significant model was identified only for the MASC subscale "thoughts" ($R^2 = 0.09$, $F = 6.20$, $p = 0.015$), with the BSL subscale "intrusions" ($\beta = -0.35$, $t = -2.50$) as a significant predictor. All additional stepwise forward linear regression analyses with the MASC total score and the subscores "emotions" and "intentions" as dependent variables revealed no significant models.

For further preliminary and exploratory data analyses, and to investigate the influence of comorbid disorders (major depression, substance abuse, eating disorders, posttraumatic stress disorder, and other personality disorders) or psychotropic medication (antidepressants or atypical neuroleptics) on MASC performance, four additional stepwise forward linear regression analyses were performed within the BPD group. Again, only one significant model was found ($R^2 = 0.13$, $F = 9.35$, $p = 0.003$), identifying PTSD ($\beta = -0.69$, $t = -3.06$, $p < 0.05$) as a significant factor influencing the ability to infer thoughts. No other stepwise forward linear regression analysis with the MASC total score and the subscales "emotions" and "intentions" as dependent variables yielded a significant model.

Thus, the preliminary and exploratory analyses revealed that comorbid PTSD and PTSD symptoms are associated with impairment in social cognition in BPD. For statistically more valid analyses of this impact, measures of social cognition were compared using an ANOVA model for the sum score and a MANOVA model for MASC subscores using Bonferroni-corrected *post hoc* comparisons between BPD patients with and without comorbid PTSD and control subjects (**Table 3**). Patients with BPD without comorbid PTSD displayed significant impairments only for the recognition of intentions compared to healthy controls (**Table 3**). By contrast, patients with BPD having comorbid PTSD displayed significant impairments on all three subscales: recognition of emotions, thoughts, and intentions, compared to healthy controls (**Table 3**). The three-group comparison (ANOVA) for the RME sum score did not reveal significant group differences ($F(2,90) = 0.28$, $p = 0.756$).

To guarantee that differences in social cognitive performance for the BPD groups with and without PTSD were not solely attributable to higher BPD symptom severity in the group with PTSD, BSL scores were compared between the two groups. An ANOVA revealed no significant difference between the two groups for the BSL total score: patients without PTSD: mean = 2.20, SD = 0.70; patients with PTSD: mean = 2.40, SD = 0.70; $F(1, 64) = 1.40$; $p = 0.241$. Of all BSL subscales, only the scale "intrusions" differed between the two groups, as assessed by a MANOVA: patients without PTSD: mean = 1.1, SD = 0.7; patients with PTSD: mean = 1.7, SD = 0.8; $F(1, 64) = 8.60$; $p = 0.005$. Also, inclusion of the BSL total score as

Table 3 | Group comparison between patients with borderline personality disorder with and without comorbid PTSD and controls in the "movie for the assessment of social cognition" (MASC).

	Patients with BPD without PTSD (*N* = 42)		Patients with BPD with PTSD (*N* = 22)		Healthy comparison subjects (*N* = 38)				*Post hoc* tests (Bonferroni)		
	Mean	SD	Mean	SD	Mean	SD	F^a	η^2	1 vs 2	1 vs 3	2 vs 3
MASC sum score	31.3	6.8	27.2	9.1	35.6	3.9	12.1**	0.20	0.053	0.012	0.000
MASC subscore emotion	10.8	2.9	9.9	3.7	11.8	1.7	3.5*	0.07	0.640	0.312	0.032
MASC subscore thoughts	3.3	0.7	2.6	1.1	3.5	0.6	9.4**	0.16	0.002	0.998	0.000
MASC subscore intentions	9.3	2.6	8.2	3.0	11.0	1.9	10.0**	0.17	0.256	0.009	0.000

PTSD, posttraumatic stress disorder; SD, standard deviation.
*[a]ANOVA model for "MASC sum score" and MANOVA model for "MASC subscores", *p < 0.05, **p < 0.01.*

a covariate in the model with two groups (BPD patients with and without PTSD) for the MASC total score (ANCOVA) and the three MASC subscores (MANCOVA) revealed no significant influence of the covariate (ANCOVA: $p = 0.552$; MANCOVA: $p = 0.785$).

INFLUENCE OF TRAUMATIC EVENTS

Development of PTSD presumes the experiencing or witnessing of traumatic events. Using the PDS scale, 31 patients with BPD (48.4%) reported experiencing a history of "accident or fire," 26 (40.6%) reported "non-sexual assault (unknown assailant)," 45 (70.3%) reported "non-sexual assault (known assailant)," 36 (56.3%) reported "sexual assault (unknown assailant)," and 37 (57.8%) reported "sexual assault (known assailant)." No sexual assault by a known assailant was reported in the control group. To assess which traumatic events have predictive value for impairments in social cognition in BPD patients, a forward stepwise linear regression with the MASC total score as dependent variable and reported trauma as independent variable was performed. Sexual assault from a known assailant ($\beta = -4.61$, $t = -2.41$, $p = 0.019$) was predictive of impairments on the MASC ($R^2 = 0.086$, $F = 5.82$). Also, the ANOVA model with the three-group comparison (BPD with and without reported sexual assault from a known assailant and controls) revealed a significant influence of group ($F(2, 102) = 13.39$, $p < 0.001$). *Post hoc t*-tests (Bonferroni corrected) indicated significantly lower MASC total scores for patients with sexual assault compared to patients without sexual assault ($p = 0.017$) and compared to controls ($p < 0.001$). Seventeen patients with BPD with comorbid PTSD (45.9%) and 20 patients with BPD without comorbid PTSD (54.1%) reported "sexual assault (known assailant)," indicating an independent risk factor in addition to comorbid PTSD for impaired social cognition.

Additionally, to guarantee that differences in social cognitive performance in the BPD groups with and without "sexual assault (known assailant)" were not solely attributable to higher BPD symptom severity in the group with a history of abuse, BSL scores were compared between the two groups. An ANOVA revealed no significant difference between the two groups for the BSL total score: patients without "sexual assault (known assailant)": mean = 2.2, SD = 0.7; patients with "sexual assault (known assailant)": mean = 2.4, SD = 0.6; $F(1, 64) = 1.65$; $p = 0.204$.

DISCUSSION

The present study comprises a systematic empirical assessment of social cognition in patients with BPD using a more ecologically valid instrument. Whereas the RME task failed to detect significant impairments in social cognition in patients with BPD, the more ecologically valid MASC clearly identified significant impairments. Patients with BPD were impaired in the recognition of the feelings, thoughts, and intentions of the starring movie characters. Thus, our results support evidence from former studies (Fonagy et al., 1996; Harari et al., 2010) and are in contrast to findings of unimpaired or enhanced social cognition abilities (e.g., Arntz et al., 2009; Fertuck et al., 2009).

The result of preserved performance on the RME task in BPD is in line with previous findings reporting no deficits in facial emotion recognition for simple tasks with no time limits or additional confounding variables (Domes et al., 2009). However, these findings stand in contrast to the finding of Fertuck et al. (2009), who reported enhanced RME performance in BPD. In the Fertuck et al. (2009) study, significantly more men were included in the control group. Men are reported to be less accurate, as well as less sensitive in labeling facial expressions (Montagne et al., 2005). Also, controls from that study performed at the lower end of the range when compared to controls from other studies using the RME task (Fertuck et al., 2009). Further, a higher percentage of Non-Caucasian participants were in the control group, whereas in the BPD group most participants were Caucasian and the RME tasks displays eye-regions of Caucasians (Fertuck et al., 2009). Our results also contradict the findings of Arntz et al. (2009) who found that borderline patients had no significant impairment in a "theory of mind" task based on completion of mental stories (Happé, 1994), compared to Cluster C patients and controls. In contrast to the advanced "theory of mind" task (Happé, 1994) applied by Arntz et al. (2009), we used the more complex and ecologically valid film material presented by the MASC. In this task, patients with BPD displayed significant impairments. These results are in line with former studies of emotion recognition, indicating that patients with BPD show deficits in the fast discrimination of negative and neutral facial expressions (Dyck et al., 2009). In addition, complex tasks for assessing emotion recognition with integrated facial and prosodic stimuli revealed impairments for patients with BPD (Minzenberg

et al., 2006). The results of impaired social cognition measured by the MASC, especially in the recognition of intentions, are in line with a previous study showing that mental state reasoning capacities are compromised in BPD (Fonagy and Bateman, 2006).

In summary, our results support the notion that higher-order integration of social information within a limited time frame is impaired in patients with BPD. Further, we extended these findings of impaired emotion recognition to thoughts and intentions, which seem to be even more impaired in BPD.

The present findings of impaired social cognition can explain several clinical symptoms of BPD. Deficits in correctly identifying the emotions, thoughts, and intentions occurring in social situations could result in fear of abandonment, alternating between extremes of idealization and devaluation of other persons, and subsequent suicidal gestures or threats. Further studies are needed to assess the cognitive and behavioral impacts of impaired social cognition in BPD.

In the present study our preliminary analyses identified three factors contributing to impaired social cognition in BPD: intrusive symptoms, comorbid PTSD, and sexual assault by a known assailant. Intrusiveness as measured by the BSL in the patient group negatively predicted outcomes on the MASC, especially for recognition of thoughts. Also, comorbid PTSD was associated with impairment in social cognition in BPD, especially for recognition of thoughts and intentions. Intrusions are core symptoms of PTSD; thus, both results argue for a negative impact of PTSD on social cognition. PTSD has been described as associated with low IQ and executive function deficits (e.g., Gilbertson et al., 2006). Both could contribute to findings of impaired social cognition in BPD patients with comorbid PTSD. Although influence of fluid IQ on social cognition was not significant in our data, further studies are needed to address this topic. Also, suppression of intrusive thoughts, which has been shown to have a negative impact on working memory (Brewin and Smart, 2005), could thereby have a negative impact on attention and thus contribute to impaired social cognition task performance in patients with comorbid PTSD. Thus, our results are in line with and extend previous findings of evidence for disturbed processing of negative or threatening visual information, as well as deviant neural responses to negative facial emotion expression in patients with PTSD (Shin et al., 2005).

Furthermore, our results provide preliminary evidence for the finding that sexual assault by a known assailant is associated with impaired social cognition. These findings are of special interest as adult BPD is associated with high rates of childhood maltreatment (Zanarini, 2000a,b). Patients with BPD report more types of abuse in childhood, beginning earlier in life, and repeated over longer periods of time than for comparison groups (Zanarini et al., 1997). As 54.1% of patients with BPD without comorbid PTSD reported sexual assault by a known assailant, this trauma with comorbid PTSD seems to be a partially independent risk factor. Nevertheless, trauma type assessment was based on the self-reported PDS scale. Thus, further studies are needed to assess more precisely the impact of trauma and trauma type on social cognition in BPD. In previous studies, severity of borderline pathology correlated with severity of childhood abuse, especially sexual abuse (Silk et al., 1995). In the present study, patients with BPD with and without PTSD, and with and without a history of sexual abuse did not significantly differ in severity of BPD symptoms. Thus, in our sample, severity of BPD did not significantly account for the finding of more impaired social cognition in comorbid PTSD or for patients with a history of sexual abuse.

Referring to the concept of the gene-environment interaction as a contributing factor to the development of psychiatric disorders, one could speculate about the genetic origins of the deficits in social cognition, as BPD has high heritability (Torgersen et al., 2008). However, our results argue for at least an additional environmental component, given that intrusions, PTSD, and sexual abuse point to the presence of environmental strains.

Interestingly, emotion dysregulation as a core feature of BPD (Sanislow et al., 2002), as assessed using the BSL, did not significantly account for impaired social cognition in our analysis within the BPD group, possibly indicating impaired social cognition as part of an independent factor of disturbed relatedness within BPD.

The findings of intrusive symptoms, comorbid PTSD, and a history of sexual abuse as predictors for impaired social cognition can be interpreted within the actual knowledge of the neural basis of social cognition.

In the present study, emotion recognition in BPD, as measured by the MASC, was less prominently impaired than recognition of intentions in the total BPD sample compared to controls. Simulation theory proposes that we can understand the mental states of others on the basis of our own mental state (Gallese and Goldman, 1998). Through recognizing the facial expression of another person we infer that person's emotional state and attribute the emotion to the encounter. This process seems to be more basal, referring less to higher cognitive functions, and is less prone to learned knowledge about social interactions (Frith and Frith, 2006). The finding of less impaired emotion recognition as compared to the recognition of intentions for the present MASC task for BPD patients indicates less impairment in this more basal social cognitive process.

Experiential learning is crucial for our ability to recognize the thoughts and intentions of others in social encounters. The temporal pole, the medial prefrontal cortex, and the adjacent paracingulate cortex seem to be involved in that process (Damasio et al., 2004). Thus, more prominent impairment in the recognition of intentions and, for patients with intrusions and comorbid PTSD, more impairment in the recognition of thoughts and intentions, may indicate that environmental factors like trauma influence these learning-dependent capacities, which might be related to deficits in the frontal lobe. Imaging data support the notion of frontal brain dysfunction in patients with BPD (Schmahl and Bremner, 2006), with possible additional impairment of frontal neural networks in BPD patients with comorbid PTSD (Driessen et al., 2004). Also, our finding of history of sexual assault by a known assailant as a predictor for impaired social cognition could represent an indicator of an invalidating environment where adequate social learning was hindered for the child while growing up.

Our study has several limitations. The results do not imply that a deficit in social cognition is specific to BPD. By contrast, such deficits have been described in a number of psychiatric disorders (e.g., euthymic bipolar patients, Montag et al., 2010; Asperger individuals, Dziobek et al., 2006). Thus, concluding from our results, follow-up studies are needed to assess social cognition abilities in PTSD patients after mono-trauma or chronic

traumatization and in individuals without PTSD after trauma, especially after sexual traumatization, to further explore our findings. Additionally, the sample size of $n = 102$ was capable of detecting only large effects with a power of 0.80. Finally, results were restricted to women with BPD.

Our data have several clinical implications. Deficits in social cognition in patients with BPD, especially with comorbid PTSD, should be considered in psychotherapy. Also, a history of sexual abuse as a predictor for impaired social cognition should be taken into account. Presumed emotions, thoughts, and intentions of interaction partners are often triggers of dysfunctional behavior in BPD. Thus, a reanalysis of these social triggers should be included in psychotherapy. Also, the emotions and cognitions of the therapist him- or herself should not be assumed to be accurately understood by the patient, but rather should be explicitly expressed. Moreover, psychotherapeutic strategies and trainings for enhancing social cognitive abilities should be integrated into the treatment of this patient group, with special respect to PTSD and traumatic experiences. Although different psychotherapeutic programs such as Dialectic Behavior Therapy, Transference Focused Psychotherapy, Schema Focused Therapy, Supportive Psychotherapy, and Mentalization-Based Therapy, which all address social cognition in their own ways, have proven effective in the treatment of BPD (de Groot et al., 2008), information on their capacities to improve social cognition is still lacking.

In summary, the present study provides additional valuable empirical evidence for impaired social cognition in patients with BPD. In particular, PTSD symptoms and sexual trauma caused by a family member or acquaintance predict poor outcomes on social cognition tasks.

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Neuronal correlates of altered empathy and social cognition in borderline personality disorder

Isabel Dziobek [a,b,*,1], Sandra Preißler [c,1], Zarko Grozdanovic [d], Isabella Heuser [b,c], Hauke R. Heekeren [a,b], Stefan Roepke [b,c,**]

[a] Max-Planck-Institute for Human Development, Lentzeallee 94, 14195 Berlin, Germany
[b] Cluster of Excellence Languages of Emotion, Freie Universität Berlin, Habelschwerdter Allee 45, 14195 Berlin, Germany
[c] Department of Psychiatry, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Eschenallee 3, 14050 Berlin, Germany
[d] Department of Radiology, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany

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ABSTRACT

Borderline personality disorder (BPD) is a severe psychiatric condition of undetermined brain underpinnings, which involves profound emotion regulation deficits and interpersonal impairment. To elucidate biopsychological markers of the disorder, we performed two studies: i.) assessing empathy and social cognition and ii.) measuring the psychophysical properties and functional brain correlates of empathic functioning in a total of fifty-one affected patients and 50 age- and gender-matched controls. In the behavioral study we applied the Multifaceted Empathy Test (MET), a new, ecologically valid measure to assess cognitive (i.e., social cognition) and emotional (i.e., empathic concern) empathy to a subset of participants. In the second study, functional Magnetic Resonance Imaging and skin conductance measurements were performed while participants took a scanner-adapted version of the MET. Patients with BPD showed impairments in cognitive and emotional empathy. Brain responses during cognitive empathy were significantly reduced in patients compared to controls in the left superior temporal sulcus and gyrus (STS/STG), where this reduction was associated with levels of intrusive symptomatology in the BPD group. During emotional empathy, patients with BPD exhibited greater brain activity than controls in the right middle insular cortex, a response that was associated with skin conductance responses in the patients. Results indicate that altered functioning of the STS/STG and insula represents pathophysiological mediators for reduced empathy in BPD, with an important role for intrusive symptomatology and levels of arousal. The findings thus support a conceptualization of BPD as involving deficits in both inferring others' mental states and being emotionally attuned to another person.

Introduction

Borderline personality disorder (BPD) is a severe psychiatric disorder with high mortality, affecting up to 5.8% of the general population (Grant et al., 2008). While in the population based studies men and women are affected in equal proportion (Grant et al., 2008), the clinical population mainly consists of young women (Zanarini et al., 2006). Despite long term impairment in social functioning in many patients (Zanarini et al., 2010), the disorder has high rates of remission of symptoms (Zanarini et al., 2006) and thus is rare after the age of mid-forties (Grant et al., 2008). BPD is characterized in the DSM-IV-TR (text revision of the Diagnostic and Statistical Manual of Mental Disorders, DSM, IV; American Psychiatric Association, 2000) by pervasive instability in moods, interpersonal relationships, and behavior. The pattern of instability in relationships has persisted for years and is in many cases closely related to disturbance in the person's early social interactions (e.g. Lobbestael et al., 2010; Preißler et al., 2010). The instability often disrupts family and professional life, and the individual's sense of self-identity. Patients with BPD often have other comorbid psychiatric disorders, one prominent among them being posttraumatic stress disorder (PTSD), which is present in up to 56% of affected individuals (e.g. Zanarini et al., 1998). In fact, BPD has been shown to be associated with childhood traumatic experiences, especially sexual abuse (Lobbestael et al., 2010). Sexual traumatic events are reported in BPD patients with PTSD (31.0%) and without PTSD (22.8%; Harned et al., 2010). High percentage of full symptom PTSD and subsyndromal PTSD (Harned et al., 2010) are reflected among others in severe suffering from intrusions in adulthood in BPD patients.

* Correspondence to: I. Dziobek, Cluster of Excellence "Languages of Emotion", Freie Universität Berlin, Habelschwerdter Allee 45, 14195 Berlin. Fax: +49 30 838 52887.
** Correspondence to: S. Roepke, Department of Psychiatry, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin, Eschenallee 3, 14050 Berlin, Germany. Fax: +49 30 8445 8365.
E-mail addresses: isabel.dziobek@fu-berlin.de (I. Dziobek), s.preissler@uni-jena.de (S. Preißler), zarko.grozdanovic@charite.de (Z. Grozdanovic), isabella.heuser@charite.de (I. Heuser), hauke.heekeren@fu-berlin.de (H.R. Heekeren), stefan.roepke@charite.de (S. Roepke).
[1] Both authors contributed equally to this article.

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BPD is largely regarded as disorder of emotion regulation (Putnam and Silk, 2005). Importantly, however, impairments in emotion regulation are also found in various affective and anxiety disorders such as posttraumatic stress disorder (PTSD), depression, or bipolar disorder (Amstadter, 2008; Taylor and Liberzon, 2007). To advance the understanding of BPD it is essential that more specific behavioral impairments and underlying neurocognitive mechanisms be identified.

More recently, the profound interpersonal impairments in BPD have been the focus of scientific study and debate (New et al., 2008), and it was argued that the unstable relational style of BPD would be the best discriminator for diagnosis (Gunderson, 2007). Yet, despite its centrality to the disorder, surprisingly little research has been devoted to interpersonal dysfunctions of BPD. In recent studies, abnormal trust and cooperation, and facial emotion recognition were identified in BPD (Domes et al., 2009; King-Casas et al., 2008).

Here we argue that impaired empathy – which comprises emotion recognition and is a fundamental prerequisite for trust and cooperation – may be a candidate for causing the dysfunctional interpersonal style in BPD. There is broad agreement that empathy comprises at least two components (Decety and Meyer, 2008; Singer, 2006). The first is a cognitive component, which captures the capacity to infer others' mental states and is also referred to as mentalizing, Theory of Mind or social cognition (Blair, 2005). Empathy also comprises an affective component, i.e., an appropriate emotional reaction to another person (Davis, 1994). In this *appropriate* response emotional empathy differs from emotional contagion or personal distress, which are self rather than other oriented and less mature emotional reactions, and can thus be conceptualized as involving emotion regulation processes in social settings. We believe that cognitive and emotional empathy can provide a powerful framework for understanding the nature and dysfunction of close relationships in BPD.

To elucidate biopsychological markers of BPD, the aims of this research were two-fold: In a first study we sought to quantify cognitive and emotional empathy in BPD patients and healthy controls simultaneously using the Multifaceted Empathy Test (MET); in a second study with an independent sample of individuals with BPD we aimed to identify for the first time the brain correlates of cognitive and emotional empathy. Based on previous work showing deficits in emotional and cognitive empathy (Ritter et al., 2011) and inferring others' complex emotions by using e.g., integrated prosodic and facial stimuli (Minzenberg et al., 2006), specifically for those patients with BPD with comorbid PTSD (Dyck et al., 2009), we predicted deficits in emotional and cognitive empathy in BPD. Given those deficits we furthermore anticipated that the BPD group would show reduced changes in BOLD signal in brain structures involved in cognitive and emotional empathy. We more specifically expected the superior temporal sulcus (STS) to show functional alterations given its important role in inferring others' mental states (Zaki et al., 2009) and given its late maturation in ontogeny (Paus, 2005), which renders it particularly vulnerable to ongoing early psychosocial stressors as experienced by most individuals with BPD. In addition, we anticipated patients with BPD to show altered functioning of the insular cortex for emotional aspects of empathy. More specifically, we expected reduced functioning of the anterior insular cortex, which has been proven a key mediator of the other-oriented sharing of the emotions (Fan et al., 2011; Lamm et al., 2011; Singer et al., 2009). Furthermore, given increased levels of personal distress in patients with BPD (Guttman and Laporte, 2000) where such self-oriented emotional reaction to others is associated with activity in the mid insular cortex (Jackson et al., 2006; Lamm et al., 2007), we expected increased activation in patients with BPD in the mid-insula.

Material and methods

Participants

In the behavioral study we included 21 women with BPD and 21 controls. In the fMRI study we included a different sample of 30 unmedicated women with BPD and 29 female controls. All participants in the fMRI task were free from psychotropic medication for at least two weeks before entering the study. In both experiments, axis I and II diagnoses were assessed by using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and the Structured Clinical Interview for DSM-IV Axis II Disorders (First et al., 1997). In addition, to quantify borderline symptoms, the Borderline Symptom List (BSL) was used (Bohus et al., 2007). Scores on the BSL indicated a similar level of symptom severity for patients of the behavioral and imaging study, respectively (cf., Table 1). Subjects with a current neurological disorder or any current medical disorder that could affect cerebral metabolism were excluded from the study. For the fMRI paradigm, patients with BPD were excluded if they had a current anorexia nervosa or substance use disorder within the last six months (cf. Table 1 for demographic data). The ethics committee of the Charité-Universitätsmedizin Berlin approved the procedure, and participants provided written informed consent.

Behavioral study

Interpersonal reactivity index (IRI)

Individual differences in cognitive and emotional trait empathy were assessed by the Perspective Taking (PT), Empathic Concern (EC), Personal Distress (PD), and Fantasy (F) scales of the Interpersonal Reactivity Index (IRI) (Davis, 1983).

Multifaceted empathy test (MET)

The Multifaceted Empathy Test (MET; Dziobek et al., 2008) is an ecologically valid measure that allows for the separate assessment of the cognitive and emotional aspects of state empathy. The MET consists of photographs depicting people in emotionally charged situations and is intended to produce strong emotional reactions (e.g., a crying child placed within a war scene).

To assess cognitive empathy, subjects are required to infer the mental states of the individuals shown in the photographs by selecting one of four mental state descriptors. To assess emotional empathy, subjects rate their level of empathic concern for the individuals displayed in the pictures on a 9-point Likert scale.

FMRI study

Multifaceted empathy test (MET) fMRI adaptation

Neuronal correlates of empathy were investigated using an fMRI adaptation of the MET (Kirchner et al., 2011). Study participants were presented with a series of 80 photographs that were taken from the original MET and supplemented by pictures from the International Affective Picture System (cf. Fig. 1) (Lang et al., 1999). To assess cognitive empathy, subjects were required to infer the mental states of the individuals shown in the photographs by selecting one of two mental state descriptors. To assess emotional empathy, subjects were requested to select "rather low" or "rather high" when asked for their level of empathic concern. The same series of pictures were presented for the cognitive and emotional empathy condition as well as for a high-level baseline control condition, in which participants were asked to make inferences about physical appearance (gender and age judgments). Because the magnitude of the BOLD response can depend on performance level and amount of effort allocated toward a task, interpretation of group differences of the BOLD response is complicated when there is a large performance difference between two groups on the same task (Bandettini et al., 1995; Weinberger and

Table 1
Demographic and clinical characteristics of patients with BPD and control subjects, respectively.

Measure	Behavioral study						fMRI study					
	Patients with BPD (n = 21)		Control subjects (n = 21)		t Value	P Value	Patients with BPD (n = 30)		Control subjects (n = 29)		t Value	P Value
	Mean	SD	Mean	SD			Mean	SD	Mean	SD		
Age in years	31.7	9.1	33.2	10.6	.50	.62	26.8	8.0	27.9	8.1	.49	.63
IQ[a]	102.1	7.1	104.5	7.6	1.34	.19	120.3	11.3	122.7	11.6	.81	.42
BDI score	37.1	8.5	3.4	0.7	−16.9	.00	34.3	11.8	6.1	6.5	−11.5	.00
BSL total score[b]	2.5	0.7					2.3	0.8				
BSL intrusion[c]	1.4	0.9					1.3	0.9				
	No.	%					No.	%				
Axis I comorbidity												
MDE Current	4	19					0					
Lifetime	6	28.6	None				13	43.3	None			
Dysthymia	7	33.3					10	33.3				
Panic disorder	0						1	3.3				
Agoraphobia	0						5	16.7				
Posttraumatic stress disorder	8	38.1					15	50				
Social phobia	1	4.8					4	13.3				
Bulimia nervosa	4	19.0					7	23.3				
Obsessive–compulsive disorder	3	14.3					3	10				
Axis II comorbidity												
Schizoid PD	1	3.1	None				0		None			
Paranoid PD	3	14.3					0					
Schizotypal PD	1	4.8					0					
Histrionic PD	1	4.8					0					
Narcissistic PD	1	4.8					1	3.3				
Antisocial PD	3	14.3					2	6.7				
Obsessive–compulsive PD	6	28.6					2	6.7				
Avoidant PD	9	42.9					8	26.7				
Dependent PD	2	9.5					1	3.3				

Abbreviations: IQ, intelligence quotient; BPD, borderline personality disorder; PD, personality disorder; BDI, Beck depression inventory.
[a] Estimated full scale IQ from vocabulary test.
[b] Between group comparison showed no group differences between the patient samples ($t(49) = .70$, $p = .49$).
[c] Between group comparison showed no group differences between the patient samples ($t(49) = .56$, $p = .58$).

Berman, 1996). Thus, pictures for the MET fMRI adaptation were chosen to be less ambiguous than in the original MET and discrimination of response alternatives was designed to be easier, so that brain imaging findings would be due to psychopathology rather than to differences in effort or performance between groups.

Levels of intrusion

To quantify levels of intrusions and to allow the assessment of relationships between intrusive memories and empathic functioning, the intrusions subscale of the Borderline Symptom List (BSL) was used (Bohus et al., 2007).

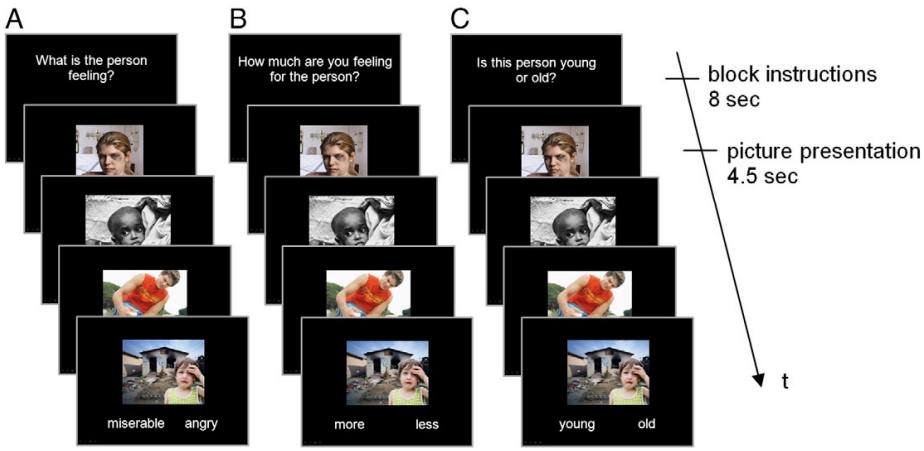

Fig. 1. Task design in A) cognitive empathy, B) emotional empathy, and C) higher-level baseline conditions. Stimuli were presented in blocks of ten. Each block was introduced by a question indicating the block type.

Experimental procedure

Stimuli were presented in a mixed blocked/event-related design using customized experimental control software (Presentation, Neurobehavioral Systems Inc., Albany, CA, http://www.neurobs.com/). Each of the 24 blocks of 10 stimuli was preceded by an introductory question (cognitive empathy: "What is the person feeling?"; emotional empathy: "How much are you feeling for the person?"; and physical appearance inference: "How old is the person/Is this person female or male?"). Each picture was presented for 4.5 s and a response pair was shown at the bottom of each picture (cf. Fig. 1). Stimuli were presented with jittered interstimulus intervals (minimum 1.25 s, maximum 21.25 s, mean 7.45 s) optimized using OptSeq2 (OptSeq; www.surfer.nmr.mgh.harvard.edu).

FMRI data acquisition and analyses

We used a 1.5-T MRI scanner (Siemens Magnetom Sonata, Erlangen, Germany) with a standard head coil to acquire whole brain MRI data. Head movement was minimized using a vacuum pad. Axially oriented functional images (T2*-weighted volumes) were acquired using standard parameters (TE: 40 ms; TR: 2500 ms; flip angle: 90°; FOV: 256 mm; matrix: 64×64; voxel size: 4×4×4 mm; 26 slices). After acquisition of functional images, two sagittally oriented T1-weighted volumes (TE: 3.56 ms; TR: 12.24 ms; flip angle: 23°; matrix: 256×256; voxel size: 1×1×1 mm) were acquired for registration of the functional images. FMRI data were analyzed using a mixed effects approach within the framework of the general linear model as implemented in FSL (FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004).

Prior to statistical analyses the following processing steps were applied: slice time and motion correction (Jenkinson et al., 2002), nonbrain removal (Smith, 2002), spatial smoothing using a Gaussian kernel of 8 mm FWHM, and high pass temporal filtering. Registration to high resolution and standard images was done using FLIRT (Jenkinson and Smith, 2001). First the subjects' T2*-weighted low resolution image was registered to the same subjects T1-weighted structural image. Then the high resolution image was registered to a program implemented standard image (a T1-weighted image in standard space, MNI 152 average image). Finally, the two transformations were combined into a third, which takes the low resolution FMRI images (and the statistic images derived from the first-level analyses) straight into standard space, when applied later, during group analysis. Time series were modeled for each individual subject using event-related regressors for the three conditions as well as for error trials and instructions, and convolved with a hemodynamic response function. Contrast images coding for the main effect of cognitive empathy (cognitive empathy vs. physical appearance inference) and emotional empathy (emotional empathy vs. physical appearance inference) were computed for each subject and, after spatial normalization, transformed into standard space (Jenkinson et al., 2002). In the higher-level analyses we report activations of a priori regions of interest as significant that exceeded an uncorrected threshold of $Z=3.09$ and had a cluster size greater than 217 mm^3 voxels. A priori regions of interest were regions that have been shown to be implicated i) in cognitive empathy and ii) in emotional empathy. Areas for cognitive empathy, i.e., the inferring of others' mental states, which is also referred to as Theory of Mind include in particular the superior temporal gyrus and medial prefrontal cortex (for reviews see e.g. Carrington and Bailey, 2009; Frith and Frith, 2005). In contrast, areas of special focus for other- and self-oriented emotional empathy are the anterior and mid parts of the insula, respectively.

To ascertain associations between individual levels of arousal and intrusions and empathic functioning, we tested whether task-induced changes in the BOLD signal in cognitive and emotional empathy would be associated with individual differences in arousal and intrusions as assessed using skin conductance reaction (SCR) measures and BSL intrusion scores. To this end, we correlated the BOLD response (parameter estimates) of the main effect for cognitive and emotional empathy, respectively, from the Region of Interests (ROIs) of contrasting activity between the BPD and control groups with the individual scores of the SCR and BSL scales. All correlation analyses were two-tailed and the alpha level was set at $P<.05$.

Psychophysiological data assessment and analyses

In the fMRI scanner, SCR activity was continuously monitored. The SCR signal was recorded digitally using an SCR processing unit (SC5, Psylab; Contact Precions Instruments, Boston, USA) outside the scanner room. For 21 patients with BPD and 24 healthy controls SCR data were usable. Data were analyzed with Matlab R2007a (The MathWorks; Massachusetts, USA). For three patients data were unavailable due to technical problems and for an additional 11 subjects no skin conductance data could be recorded due to marginal sweat production or excessive cornea production.

The SCR time series was analyzed using the mean amplitude and mean descent speed within each block. The time series was first high-pass filtered (Butterworth filter of order 4 at 0.01 Hz) to remove the slow drifts associated with the drying gel. The cutoff frequency (0.01 Hz) corresponds roughly to a 90 s window and was chosen conservatively to remove only very slow drifts. The time series where then z-transformed and the mean activation was computed for each block and subject.

To study the duration of SCR responses, we considered the average descent speed of the time series in each block. The descent speed is given by the negative values of the first derivative in the continuous case. To assess an approximation of the first derivative, the time series were convolved with the first derivative of a Gaussian ($\sigma=50$ ms). Given comparable amplitudes for the spikes in SCR activity, the descent speed is inversely proportional to the duration of the event. With its robustness to overlapping events, the mean descent is a measure of event duration that is especially well suited for the MET fMRI adaptation with its relatively fast-changing pictures.

To control for trends and habituation, the slope of a linear least square fit to the mean SCR activation in each trial was used, over the course of each run. An independent sample t-test of the slope between the control group ($M=0.029$; $SD=0.091$) and the BPD group ($M=0.021$; $SD=0.086$) did not reveal significant differences ($t\ (144)=0.54$; $p=.58$).

Results

Behavioral study

Patients with BPD from Study 1 showed trends toward lower scores than controls on the emotional scales (EC and PD) and on the PT scale of the IRI (Davis, 1983). On the more objective and ecologically valid Multifaceted Empathy Test (MET) (Dziobek et al., 2008) patients with BPD showed significant impairments in both facets of empathy compared to healthy controls (Table 2). Within group correlation analyses between the cognitive and emotional scales of the MET showed a positive, albeit non-significant, association in the patient group ($r=.34$, $p=.13$), whereas controls showed a small and non-significant negative correlation ($r=-.12$, $p=.59$).

Functional MRI

Behavior

As expected, behavioral data of the adapted easier fMRI version of the MET showed no significant group effect for cognitive or emotional empathy ratings or reaction times, suggesting that both groups showed similar engagement in the experimental design as required (Table 3).

Table 2
Emotional and cognitive empathy in the behavioral study.

Measure	Patients with BPD (n=21)		Control subjects (n=21)		t Value	P Value
	Mean	SD	Mean	SD		
IRI						
Cognitive empathy						
Perspective taking	21.75	6.25	25.00	3.67	1.88	.07
Fantasy	27.00	4.80	26.00	4.90	0.59	.56
Emotional empathy						
Empathic concern	23.90	6.90	28.24	2.08	1.99	.06
Personal distress	25.00	5.50	17.50	4.30	3.85	.00
Behavioral MET performance						
Cognitive empathy	20.95	2.52	22.3	1.32	2.12	.03
Emotional empathy	4.87	2.13	6.00	1.20	2.22	.04

Abbreviations: BPD, borderline personality disorder; IRI, Interpersonal Reactivity Index; MET, Multifaceted Empathy Test.

Correlation analyses revealed positive associations between the cognitive and emotional scales of the MET in individuals with BPD ($r=.45$, $p=.02$) but not in the control group ($r=.05$, $p=.79$).

Skin conductance

Analyses of SCR duration during the different conditions of the fMRI experiment showed no effect of condition for the healthy controls, $F(2,22)=1.52$, $p=.24$, and for patients with BPD, $F(2,19)=1.76$, $p=.20$. The same patterns were also found for SCR amplitude in the control group, $F(2,22)=0.61$, $p=.55$, and for patients with BPD, $F(2,19)=2.64$, $p=.10$. Moreover, there was no group effect for SCR duration or SCR amplitude during the different MET conditions (Table 4).

FMRI main effects

Cognitive empathy

Separate mixed effect group analyses for patients with BPD and healthy controls, contrasting cognitive empathy with a higher-level baseline, revealed activations in areas that typically respond to social cognition such as the superior temporal sulcus and gyrus (STS/STG) extending into the temporal parietal junction bilaterally, the orbito-frontal cortex, temporal pole, and paracingulate gyrus. For both groups a similar pattern of activations occurred (Table 5).

Emotional empathy

The comparison of emotional empathy and higher-level baseline revealed similar activations for the BPD and control groups. Increases in the BOLD response were found among others in the inferior frontal cortex, STS/STG, and insular cortex (Table 6).

Table 3
Behavioral results during the fMRI experiment.

Measure	Patients with BPD (n=28[a])		Control subjects (n=29)		t Value (df=55)	P Value
	Mean	SD	Mean	SD		
fMRT MET performance						
Cognitive empathy	.96	.07	.97	.06	−.99	.33
Emotional empathy	1.5	.18	1.6	.18	−1.26	.21
Higher-level baseline	.94	.06	.95	.03	−.53	.60
Reaction time[b]						
Cognitive empathy	2228.4	303.9	2136.3	285.9	1.18	.24
Emotional empathy	2170.3	335.9	2159.1	313.7	.13	.90
Higher-level baseline	1683.4	255.0	1605.0	264.0	1.14	.26

Abbreviations: BPD, borderline personality disorder; MET, Multifaceted Empathy Test.
[a] Outlier analysis resulted in the exclusion of two patients with BPD to satisfy the assumption of a normal distribution.
[b] Reaction time is given in msec.

Table 4
Skin conductance reaction (SCR, duration and amplitude).

Measure	Patients with BPD (n=21)		Control subjects (n=24)		t Value	P Value
SCR	Mean	SD	Mean	SD		
Duration[a]						
Cognitive empathy	.0009	.00074	.0009	.00044	.01	.99
Emotional empathy	.0011	.00064	.0011	.00058	.26	.80
Higher-level baseline	.0010	.00068	.0011	.00052	.42	.68
Amplitude[b]						
Cognitive empathy	.0093	.03200	.0083	.04976	.08	.94
Emotional empathy	.0257	.04769	.0167	.05201	.60	.55
Higher-level baseline	.0008	.06438	.0256	.07284	1.20	.23

Abbreviations: BPD, borderline personality disorder; SCR, skin conductance reaction.
[a] Modulus of the first derivative of z-transformed and filtered SCR values (to indicate decay of SCR, only negative values were used).
[b] z-transformed and filtered.

Group differences

Cognitive empathy

Contrasting brain activity in cognitive empathy (MET cognitive empathy vs. MET higher-level baseline) between patients with BPD and controls, we found greater changes in the BOLD signal in the left STS/STG (MNI coordinates: −58, −44, 8, z=3.11) in the control group (Fig. 2A), where this finding seems to be specific to cognitive empathy (cf. Fig. 2B).

Associations with level of intrusions. Correlation analyses revealed that the left STS/STG ROI of contrasting activity between the BPD and control group during cognitive empathy (using mean activation in the detected cluster) was associated with levels of intrusions as measured by the BSL in the BPD group ($r=-.42$, $p=.02$; cf. Fig. 2C).

Emotional empathy

By contrasting the brain activity in emotional empathy (MET emotional empathy vs. MET higher-level baseline) between patients with BPD and healthy controls, we found greater increases in the BOLD signal in the right insular cortex (MNI coordinates: 34, −12, 14, z=3.14) and the right STS (MNI coordinates: 68, −28, 0, z=3.32) in the patient group (Fig. 3A). This finding seems to be specific to emotional empathy (Fig. 3B).

Associations with skin conductance response. We found that changes in the BOLD signal in the right insular cortex ROI of contrasting activity between the BPD and control groups during emotional empathy (using mean activation in the detected cluster) correlated with levels of arousal as measured by the SCR in the BPD group ($r=-.43$, $p=.05$) but not in the controls (Fig. 3C).

Discussion

This study reports for the first time cognitive and emotional empathy functions and their neuronal correlates in individuals with BPD. Using a novel task, we found patients with BPD to be impaired in both facets of empathy. In an fMRI study with an independent sample, we found that individuals with BPD showed less activation than controls in the STS/STG region during cognitive empathy, where this reduced activation was associated with levels of intrusion in the patients. Moreover, we found greater changes in the BOLD signal in the middle insula region in the patients during emotional empathy, where this activation reflected levels of arousal.

Table 5
Main effect of cognitive empathy in patients with BPD and control subjects.

Patients with BPD (n = 30)							Control subjects (n = 29)						
		MNI-coordinates							MNI-coordinates				
Brain region	H	x	y	z	z-score	Volume, mm³	Brain region	H	x	y	z	z-score	Volume, mm³
Orbitofrontal cortex (extending to STS)	L	−48	28	−4	5.45	10,544	STS	L	−58	−42	4	8.33	18,678
Occipital pole	L/R	24	−92	−4	4.29	2265							
Orbitofrontal cortex	R	50	30	−2	4.63	2090	Orbitofrontal cortex	R	56	26	−2	5.38	1826
Posterior STS	R	56	−36	−2	4.34	824	STS	R	58	−48	10	6.23	2216
Anterior STS	R	56	−6	−18	4.51	449							
Paracingulate gyrus	L/R	−2	12	52	4.25	738	Paracingulate gyrus	L/R	−6	16	52	5.03	1186
							Caudate	L	51	65	40	4.94	1161
							Brainstem (mesencephalon)	L/R	10	−26	−12	4.57	898
Posterior cingulate gyrus	L/R	0	−34	40	−4.52	1280	Posterior cingulate gyrus	L/R	4	−36	40	−6.08	1418
Angular gyrus	R	48	−44	44	−3.99	1054	Angular gyrus	R	42	−68	42	−5.82	3810
							Precuneus cortex	L/R	8	−64	38	−4.26	744
							Middle frontal gyrus	R	32	28	44	−5.13	562
							Central opercular cortex extending to insular cortex	L	−50	−8	4	−4.65	542
							Frontal pole	L/R	8	60	−2	−4.42	526

Abbreviations: BPD, borderline personality disorder; MNI, Montreal Neurological Institute; H, hemisphere; L, left; R, right; IC, insular cortex; STS, superior temporal sulcus.

BPD pattern of empathic functioning

To elucidate biopsychological markers of BPD we assessed empathy using our newly developed and validated Multifaceted Empathy Test (MET; Dziobek et al., 2008), which allows the simultaneous measurement of cognitive and emotional empathy in an ecologically more valid fashion than current questionnaires do. In the behavioral study (study 1) we found that individuals with BPD were impaired in both cognitive and emotional empathy as measured by the MET. We found only a trend for decreased empathic functioning in BPD as measured with the Perspective Taking and Empathic Concern Scale of the IRI. However, self-report measures such as the IRI require introspection, which is reduced in BPD (Levine et al., 1997), likely limiting the ability to accurately describe personality on questionnaires. The photorealistic MET, given its higher ecological validity and reliance on performance scores, is less abstract and avoids the possible confounds encountered when using questionnaires.

We found reduced cognitive empathy (i.e., a key component of social cognition) in individuals with BPD. The results seem somewhat at odds with research on emotion recognition abilities, which has shown grossly unaffected performance for individuals with BPD (Domes et al., 2009). Higher-order social processing, such as the integration of facial and prosodic stimuli, however, results in emotion recognition deficits in BPD (Minzenberg et al., 2006). Moreover, it was suggested that individuals with BPD tend to misread others' minds when in intense interpersonal encounters (Fonagy and Bateman, 2008), often when emotionally aroused (Wolff et al., 2007). The design of the MET entails both (a) more complex higher-order social processing than simple emotion recognition tasks and (b) by asking the participants to get emotionally involved with the distressed people in the pictures and an embedding of mindreading functions in a relevant and arousing interpersonal setting.

In the BPD group we not only found reduced cognitive but also emotional empathy. We further found positive correlations between the two empathy facets in the patients, where those associations reached significance in the imaging study only, likely due to the higher number of participants. This might provide evidence for both (a) the suggestion that the misinterpretation of the mental states of others leads to extreme and dysfunctional emotional responses in social interactions (New et al., 2008), and (b) that emotional arousal causes impairments in interpreting others' mental states (Wolff et al., 2007).

Table 6
Main effect of emotional empathy in patients with BPD and control subjects.

Patients with BPD (n = 30)							Control subjects (n = 29)						
		MNI-coordinates							MNI-coordinates				
Brain region	H	x	y	z	z-score	Volume, mm³	Brain region	H	x	y	z	z-score	Volume, mm³
Paracingulate gyrus (extending in inferior frontal cortex and anterior IC L)	L/R	2	34	26	5.11	11,996	Inferior frontal cortex (extending to anterior IC)	L	−52	24	−6	6.68	13,051
Inferior frontal cortex (extending to anterior IC)	R	52	20	4	4.27	2026	Inferior frontal cortex (extending to anterior IC)	R	54	20	18	5.18	1703
Lateral occipital cortex (extending to STS)	L	−60	−58	10	4.3	1273	Posterior STS	L	−60	−44	6	5.42	1592
Intracalcarine cortex	R	10	−78	8	4.3	818							
Intracalcarine cortex	L	−10	−70	−4	3.9	468							
Posterior cingulate cortex (extending to Precuneous Cortex)	L/R	−2	−52	28	3.5	426							
							Brainstem (mesencephalon)	L/R	−4	−20	−28	4.18	548
							Temporal lobe (extending to posterior insular cortex)	R	60	−52	−14	−4.64	1748
							Secondary somatosensory cortex	R	62	−24	36	−4.76	1269
							Heschels gyrus (extending in posterior insula cortex)	L	−50	−10	4	−4.12	980
							Posterior cingulate cortex	R	8	−32	44	−4.27	363

Abbreviations: BPD, borderline personality disorder; MNI, Montreal Neurological Institute; H, hemisphere; L, left; R, right; IC, insular cortex; STS, superior temporal sulcus.

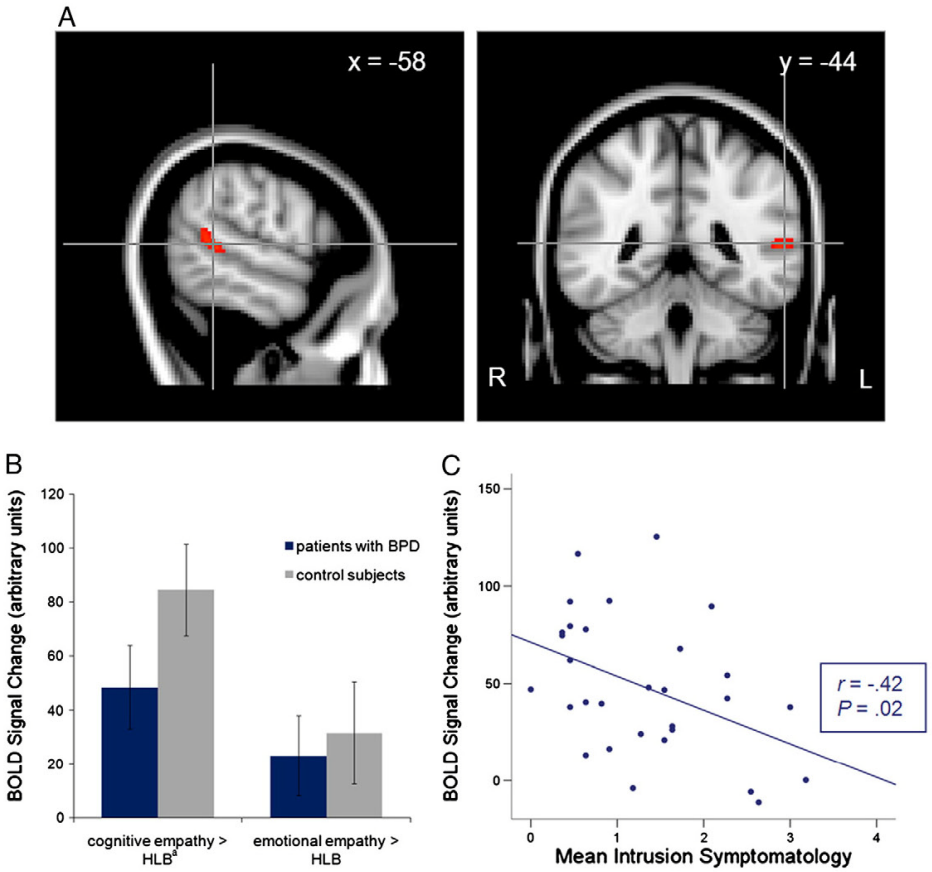

Fig. 2. A) Contrasts of cognitive empathy vs. higher-level baseline (HLB) conditions yielded greater activity in controls (N = 30) than in patients with BPD (N = 29) in the left superior temporal sulcus (STS) (Montreal-Neurological-Institute coordinates: 58, −44, 8, $p = .005$). Highlighted areas indicate regions where differences in blood oxygen level dependent (BOLD) signal between groups were significant. B) Bar graphs show BOLD signal change in left STS/STG in both empathy conditions (relative to HLB) for each group. Error bars represent standard error of the mean. (Montreal-Neurological-Institute coordinates of peak voxel, −58, −44, 8, Region of interest at $p = .005$). [a]Contrasts were used in the ROI selection process; significant difference between groups ($t(57) = -4.93$, $p < .001$). C) Cognitive empathy (relative to higher-level baseline) responses in the left STS/STG (Montreal-Neurological-Institute coordinates of peak voxel, −58, −44, 8, Region of interests at $p = .005$) were negatively correlated with mean intrusion symptomatology measured by Borderline Symptom List (Bohus et al., 2007) in the BPD group (N = 29).

Neurocognitive and psychophysiological markers of empathy in BPD

To the best of our knowledge this is the first study that looked at the neuronal correlates of cognitive and emotional facets of empathy simultaneously in individuals with and without BPD. Both groups activated similar networks when inferring the mental states of others. Those networks closely resembled brain activation patterns found in previous social cognition studies, and involved the temporal pole, the STS/STG, and the superior frontal gyrus (for a review, see Frith and Frith, 2005). Emotional empathy activated a comparable network of brain areas, in addition comprising the insula and medial prefrontal cortex (MPFC) bilaterally. Those findings are in line with other studies investigating empathic concern (Singer and Lamm, 2009).

Contrasting brain activation during cognitive empathy between groups revealed a cluster of voxels in the left posterior STS/STG to be more activated in the controls than in the individuals with BPD. The STS is known for its role in social cognition and is an important part of the neuronal network that mediates thinking about others (Saxe and Kanwisher, 2003). Research in attachment in BPD suggests that maltreatment in childhood leads to the inhibition of mentalizing abilities in affected individuals (Fonagy et al., 1996), which might be reflected in decreased activity in the STS. Childhood maltreatment by a caregiver such as emotional neglect or sexual abuse is in fact one of the most important psychosocial risk and prognostic factors for BPD symptomatology (Zanarini et al., 2006), possibly accounting for the high comorbidity of PTSD in BPD patients (McGlashan et al., 2000). We found that task-induced changes in the BOLD signal in the STS/STG region were associated with individual differences in levels of intrusions present in the individuals with BPD: those individuals showing particularly low levels of activation in the STS/STG region reported high levels of recurring traumatic memories. Childhood maltreatment likely has effects on the developing brain. Interestingly, the STS region matures late in ontogeny (Paus, 2005), rendering it particularly vulnerable to ongoing early psychosocial stressors. The behavioral consequences of those neuronal changes may consist of difficulties in inferring the mental states of others. The recent finding of impaired emotion recognition abilities in BPD patients with comorbid PTSD, which is in line with the findings of the current study, further points out the relevance of intrusive memories for empathic functions (Dyck et al., 2009).

While brain activation during emotional empathy did not differ between groups in the anterior insula, a cluster of voxels in the right mid-insula was more activated in the individuals with BPD than in the controls. The mid-insula has been shown to react strongly to bodily

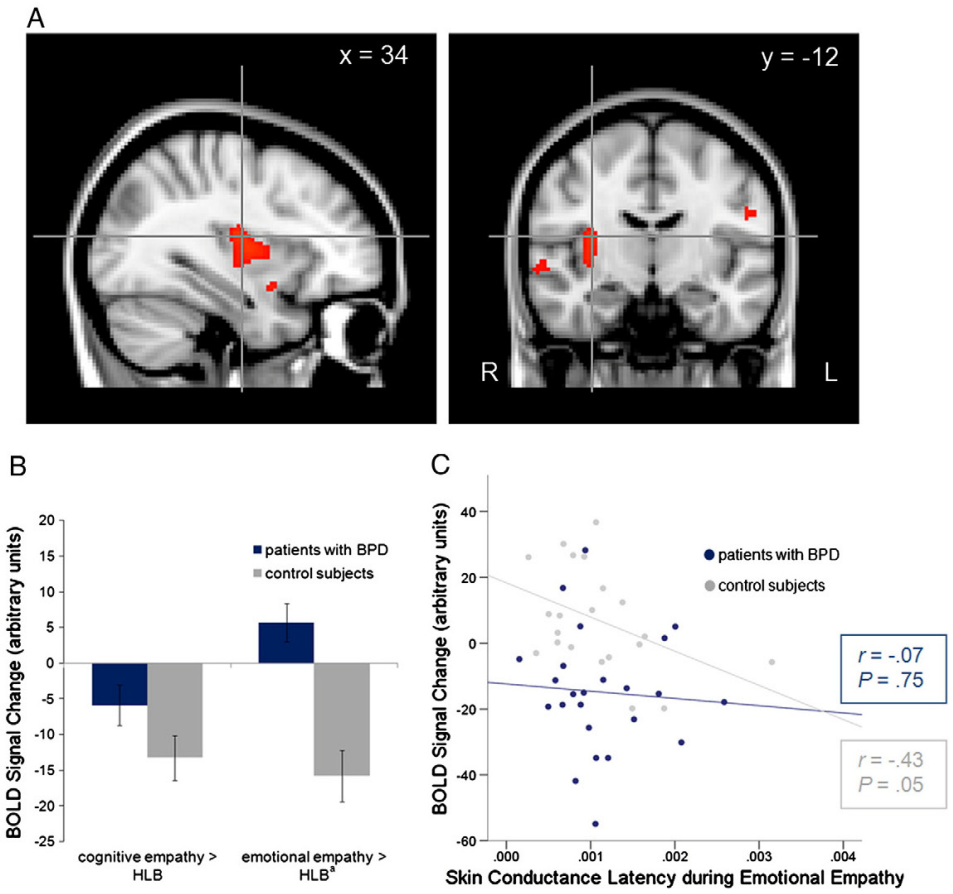

Fig. 3. A) Contrast of emotional empathy vs. higher-level baseline (HLB) conditions yielded greater changes in BOLD signal in patients with BPD (N = 29) than in controls (N = 30) in the right insular cortex (Montreal-Neurological-Institute coordinates: 34, −12, 14, $p = .005$). Highlighted areas indicate regions where the difference in blood oxygen level dependent (BOLD) signal between groups was significant. B) Bar graphs show BOLD signal change in right insular cortex in both empathy conditions (relative to HLB) for each group. Error bars represent standard error of the mean. (Montreal-Neurological-Institute coordinates of peak voxel, 34, −12, 14, Region of interest at $p = .005$). [a]Contrasts were used in the ROI selection process; significant difference between groups ($t(57) = 4.54$, $p < .001$). C) Emotional empathy (relative to higher-level baseline) responses in the right insular cortex (Montreal-Neurological-Institute coordinates of peak voxel, 34, −12, 14, Region of interests at $p = .005$) were negatively correlated with mean arousal measured by duration of skin conductance reaction (SCR) during emotional empathy in the BPD group (N = 21; controls: N = 24). Latency of SCR is measured by modulus of the first derivative of z-transformed and filtered SCR values. To indicate decay of SCR only negative values were used.

states of arousal (Brendel et al., 2005). Our finding of positive associations between activation in the right middle insula and skin conductance responses in the individuals with BPD indeed supports the notion of increased arousal during emotional empathy. Interestingly, emotional empathy, given that it requires an other-oriented appropriate emotional response, can in part be conceptualized as an emotion regulatory process in interpersonal settings. The inability of individuals with BPD to regulate their emotions toward others (e.g., Putnam and Silk, 2005) might be reflected in increased arousal and personal distress. In fact, the tendency to experience personal distress in response to the suffering of others has been associated with mid-insular activation in healthy subjects (Decety and Moriguchi, 2007). Higher prevalence of personal distress has been reported for individuals with BPD previously (Guttman and Laporte, 2000) and was also found in the current study as measured by the Personal Distress scale of the IRI. This might as a result represent the reason for reduced behavioral empathic concern in BPD. Thus, the relationship between empathic concern and personal distress, the latter being mediated by the mid-insular cortex, is likely that of an inverted U-shaped function: while at low levels arousal and personal distress can be considered as important precursors to the more mature empathic concern, they seem detrimental and a reflection of reduced emotion regulation functions at very high levels. Other studies have provided evidence that individuals who can regulate their emotions are more likely to experience concern for others (Eisenberg et al., 1994). In fact, it is reasonable to assume that emotional reactions to another person's affective state require control for the emergence of empathy. Without such control, the activation of a perception–action mechanism, including the associated autonomic and bodily responses, could lead to emotion contagion and personal distress.

Along with the insula we also found the right anterior STS/STG region to be activated more in the patient group than in the controls when engaging in emotional empathy. While the posterior STS, particularly in the left hemisphere, has been reported as a prime area for mentalizing (Hein and Knight, 2008), the right STS has been shown to be sensitive to the perceived congruency between a person's action and his/her emotional expression (Wyk et al., 2009). Thus, increased activation of the right STS/STG during emotional empathy might indicate that patients with BPD mistrust the truthfulness of others' emotional reactions. This is in line with recent research on

reduced trust in affected individuals (King-Casas et al., 2008; Unoka et al., 2009) and further supports the notion that individuals with BPD have problems interpreting others' emotions when emotionally aroused (Wolff et al., 2007).

Conclusions

In summary, we propose that deficits in cognitive and emotional empathy are central to BPD. Our results indicate that the misinterpretation of others' mental states might provide an explanation for dysfunctional emotional responses in interpersonal settings in BPD, where such relationship needs to be investigated in future studies. Furthermore, the results suggest that levels of intrusions might play an important role in the emergence of impaired mentalizing in BPD and that the STS is a pathophysiological mediator for such a deficit. The insula was identified as a crucial brain area for reduced emotional empathy in BPD, likely reflecting high levels of arousal and personal distress. As such, BPD can be conceptualized as involving deficits in both inferring mental states and being emotionally attuned to another person.

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Lack of empathy in patients with narcissistic personality disorder

Kathrin Ritter [a,*], Isabel Dziobek [b,e,f], Sandra Preißler [a], Anke Rüter [a], Aline Vater [a], Thomas Fydrich [c], Claas-Hinrich Lammers [d], Hauke R. Heekeren [b,e,f], Stefan Roepke [a,e,*]

[a] Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, Department of Psychiatry, Berlin, Germany
[b] Max-Planck-Institute for Human Development, Neurocognition of Decision Making Group, Berlin, Germany
[c] Humboldt University Berlin, Institute of Psychology, Berlin, Germany
[d] Asklepios Clinic North — Ochsenzoll, Hamburg, Germany
[e] Cluster of Excellence "Languages of Emotion", Freie Universität Berlin, Berlin, Germany
[f] Freie Universität Berlin, Department of Education and Psychology, Berlin, Germany

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ABSTRACT

The study's objective was to empirically assess cognitive and emotional empathy in patients with narcissistic personality disorder (NPD). To date, "lack of empathy" is a core feature of NPD solely based on clinical observation. The study's method was that forty-seven patients with NPD, 53 healthy controls, and 27 clinical controls with borderline personality disorder (BPD) were included in the study. Emotional and cognitive empathy were assessed with traditional questionnaire measures, the newly developed Multifaceted Empathy Test (MET), and the Movie for the Assessment of Social Cognition (MASC). The study's results were that individuals with NPD displayed significant impairments in emotional empathy on the MET. Furthermore, relative to BPD patients and healthy controls, NPD patients did not show deficits in cognitive empathy on the MET or MASC. Crucially, this empathic profile of NPD is not captured by the Structured Clinical Interview for DSM-IV for Axis II Disorders (SCID-II). The study's conclusions were that while NPD involves deficits in emotional empathy, cognitive empathy seems grossly unaffected.

1. Introduction

Narcissistic personality disorder (NPD) is characterized by a "lack of empathy" as well as a pervasive pattern of grandiosity and need for admiration (American Psychiatric Association, 2000). It is a severe mental disorder with prevalence rates of up to 6% in the general population (Stinson et al., 2008; Ritter et al., 2010), severe functional impairment (Miller et al., 2007; Stinson et al., 2008), and high suicide rates (Pompili et al., 2004). Although narcissism as a personality trait and empathy have been shown to be negatively correlated (e.g., Watson et al., 1984; Watson and Morris, 1991; Watson et al., 1992; Porcelli and Sandler, 1995) the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criterion "lack of empathy" in NPD is solely based on clinical observation and expert consensus (also personal communication with E. Ronningstam) (Kohut, 1966; Kernberg, 1970; Akhtar and Thomson, 1982; Millon, 1983). Thus, to date, a congruent conceptualization and empirical evaluation of the criterion "lack of empathy" in NPD are lacking. Therefore, the aim of the study was to empirically assess empathy in patients with NPD according to DSM-IV.

When NPD first appeared in the official psychiatric nomenclature in the Diagnostic and Statistical Manual of Mental Disorders-Third Edition (DSM-III) in 1980 (American Psychiatric Association, 1980) "lack of empathy" was established as a sub-criterion of the fifth criterion "characteristic disturbances in interpersonal relationships" (p. 317). Although DSM-III-based studies revealed that the criterion "lack of empathy" lacked discriminant validity (Morey, 1985; Gunderson et al., 1991; Gunderson and Ronningstam, 2001) (i.e., it had multiple significant correlations across other personality disorders; PDs), and offered poor interrater reliability (Pfohl et al., 1986) it was established as a separate criterion in the DSM-III-R (criterion 8), describing the "inability to recognize and experience how others feel" and was also maintained in the DSM-IV (American Psychiatric Association, 1994) and Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) as criterion 7. Further studies based on the DSM-IV additionally revealed low diagnostic specificity of the criterion "lack of empathy" (Blais et al., 1997; Holdwick et al., 1998; Gunderson and Ronningstam, 2001; Fossati et al., 2005).

In summary, weak empirical evidence of convergent and divergent validity of the DSM criterion "lack of empathy" stands in sharp contrast

* Corresponding authors. Department of Psychiatry, Charité — Universitätsmedizin Berlin, Campus Benjamin Franklin, Eschenallee 3, D-14050 Berlin, Germany, EU. Tel.: +49 30 8445 8703; fax: +49 30 8445 8757.
E-mail addresses: kathrin.ritter@charite.de (K. Ritter), stefan.roepke@charite.de (S. Roepke).

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to longstanding clinical (mostly psychoanalytic) case descriptions and the conceptualization of NPD (Kohut, 1966; Kernberg, 1970; Akhtar and Thomson, 1982; Millon, 1983). Our hypothesis is that this contradiction is due to the fact that no theoretical construct underlies the NPD criterion "lack of empathy" in the DSM (Millon, 1983), and thus, its assessment may be insufficient.

Research has already proposed a multidimensional model of empathy (Davis, 1983; Blair, 2005a), comprising two distinct but related constructs: cognitive and emotional empathy. A third dimension of motor empathy (Blair, 2005a) was later incorporated into the model of emotional empathy (Preston and de Waal, 2002). Thus, cognitive empathy (Baron-Cohen and Wheelwright, 2004) refers to the ability to take another person's perspective and to represent others' mental states, and as such, broadly overlaps with the constructs "Theory of Mind" (Premack and Woodruff, 1978) and "mentalizing" (Frith and Frith, 2003). The construct of emotional empathy (Mehrabian and Epstein, 1972; Eisenberg and Miller, 1987) describes an observer's emotional response to another person's emotional state. Based on the multidimensional facet model of empathy, our group recently developed the Multifaceted Empathy Test (MET, Dziobek et al., 2008), a task presenting photorealistic stimulus material and simultaneously assessing both cognitive and emotional empathy in a more ecologically valid manner than previous self-rating questionnaires. To further differentiate aspects of cognitive empathy we developed the Movie for the Assessment of Social Cognition (MASC, Dziobek et al., 2006), a film-based task depicting social interactions, demanding the understanding of the emotions, thoughts, and intentions of movie characters.

To ascertain the specificity of a "lack of empathy" in NPD, we used a clinical comparison group of patients with borderline personality disorder (BPD) according to DSM-IV in which impaired cognitive empathy and unimpaired emotional empathy were found. We also compared both clinical groups to healthy controls (Fonagy et al., 1996; Harari et al., 2010).

1.1. Aims of the study

The current study was conducted, first, to empirically assess cognitive and emotional empathy in a clinical sample of patients with NPD, and second, to compare the results to a clinical comparison group of patients with BPD. We hypothesized that patients with NPD would show significantly higher impairments in cognitive and emotional empathy compared to healthy controls. Compared to patients with BPD, we hypothesized significant impairment in emotional empathy and no difference in cognitive empathy for the NPD group. The third aim was to evaluate the convergence of the DSM-IV criterion "lack of empathy" with the empirical measures used in this study.

2. Materials and method

2.1. Sample

Forty-seven inpatients with NPD were recruited from the Department of Psychiatry, Charité — Universitätsmedizin Berlin and cooperating German hospitals. Fifty-three age- and gender-paralleled healthy comparison subjects were recruited via media advertisements.

Previous studies of NPD and BPD have reported substantial comorbidity (Westen et al., 2006) between the two disorders and found overlap in the symptoms of affect dysregulation, impulsivity, and unstable relationships (Morey, 1988; Ronningstam and Gunderson, 1991; Blais et al., 1997). To show the more specific character of "lack of empathy" for NPD, we assessed a clinical comparison group with 27 BPD patients without comorbid NPD from the Department of Psychiatry, Charité — Universitätsmedizin Berlin. All BPD patients were inpatients and on a waiting list for an inpatient treatment program prior to admission, and none was admitted for acute care. Axis II diagnoses of patients and controls were assessed with the Structured Clinical Interview for DSM-IV for Personality Disorders (SCID-II, First et al., 1997, German version: Fydrich et al., 1997) by trained psychiatrists or psychologists. Interrater reliability of SCID-II diagnoses was assessed ($N=8$) with a pairwise interview design. Interviewers were blind to PD diagnoses. Kappa was acceptable with $\kappa=0.797$ for NPD diagnosis and $\kappa=0.820$ for BPD diagnosis. For the NPD criterion "lack of empathy," however, Kappa showed a perfect agreement, $\kappa=1.0$. Internal consistencies for NPD items (Cronbach's $\alpha=0.896$) and BPD items (Cronbach's $\alpha=0.876$) were good. Axis I comorbidity was assessed with the Structured Clinical Interview for DSM-IV for Axis I Disorders (First et al., 1996, German version: Wittchen et al., 1997) in the NPD sample and with the Mini International Neuropsychiatric Interview (M.I.N.I., Sheehan et al., 1998, German version: Lecrubier et al., 1998) in the BPD sample. Exclusion criteria for all patients were history of psychotic disorder, a current bipolar I or II disorder, a current manic or hypomanic episode, or substance induced disorder (e.g., intoxication or withdrawal syndrome). All procedures were approved by the Human Subjects and Ethics Committee of Charité — Universitätsmedizin Berlin. Written informed consent was obtained from each participant. Socio-demographic and clinical data are presented in Table 1.

2.2. Psychometric assessment instruments

To assess psychopathology, the general severity index (GSI) of the Symptom Checklist 90 Revised (SCL-90-R, Derogatis, 1977, German version: Franke, 2002) was calculated. The internal consistency for the GSI was good (Cronbach's $\alpha=0.989$). For IQ screening, subtest 4 (recognizing rules) of the well-established German "Leistungs-Prüf-System" (LPS, Horn, 1983) was administered.

2.3. Measures of cognitive and emotional empathy

The Interpersonal Reactivity Index (IRI; Davis, 1983; German version: Paulus, 2006) was employed as a multidimensional self-report estimate of empathy. In this study we focus on the scales "perspective taking" (the ability to assume another individual's point of view) and "empathic concern" (the capacity to experience sympathy for others). An example perspective-taking item is: "When I'm upset at someone, I usually try to 'put myself in his shoes' for a while." An example empathic-concern item is: "I often have tender, concerned feelings for people less fortunate than me." The IRI has been shown to correlate with other measures of empathy, providing support for the construct validity of the measure (Davis, 1980). Both subscales have good internal consistencies (perspective taking: $\alpha=0.747$, empathic concern: $\alpha=0.776$). In the sample of all participants of the present study both scales correlate moderately with $r=0.457$, $P<0.001$ (NPD: $r=0.322$, $P=0.144$, BPD: $r=0.534$, $P=0.004$; healthy controls: $r=0.398$, $P=0.004$).

The Multifaceted Empathy Test (MET, Dziobek et al., 2008) is a PC-assisted test consisting of photographs that show 23 pairs of picture stimuli with people in emotionally charged situations. To assess cognitive empathy, participants were required to infer the mental state of the subject in the photo, and were asked to indicate the correct one from a list of four. After giving feedback about the displayed people's actual mental states, emotional empathy was assessed. First, participants were required to rate the amount of mirroring of an emotion (i.e., emotional contagion) that took place in response to a picture (e.g., if the mental state of the person was anxious, subjects were asked to rate how anxious they felt). Participants indicated their responses on a visual analogue scale ranging from 0 to 9 (0 = not at all, 9 = very much). As an additional measure of more mature emotional empathy, subjects were also asked to rate the degree of empathic concern they felt for the person in the picture (visual analogue scale, 0 = not at all, 9 = very much). All pictures were presented in two forms: First, all emotionally charged situations (background) were presented without a person; then, in a second step, all of the situations were presented with a person expressing a relevant emotion. All background pictures were first independently rated for arousal in order to enable us to control for this general level of arousal when establishing group differences in empathic processing. Internal consistency of the MET's scales ranged from $\alpha=0.71$ to $\alpha=0.92$, and convergent and divergent validity were highly satisfactory (Dziobek et al., 2008). In the study sample, the scales emotion recognition and empathic concern were not correlated (All: $r=0.146$, $P=0.150$; NPD: $r=0.125$, $P=0.578$, BPD: $r=0.297$, $P=0.140$; healthy controls: $r=-0.071$, $P=0.626$); nor were the scales emotion recognition and mirroring emotions (All: $r=0.114$, $P<0.265$; NPD: $r=-0.034$, $P=0.879$, BPD: $r=0.362$, $P=0.069$; healthy controls: $r=-0.137$, $P=0.341$). MET cognitive empathy was not correlated with emotional empathy assessed by the MET either for healthy controls (for empathic concern: $r=-0.071$, $P=0.626$, for mirroring emotions: $r=-0.137$, $P=0.341$) or for NPD patients (for empathic concern: $r=-0.010$, $P=0.949$; for mirroring emotions: $r=-0.020$, $P=0.893$).

To assess cognitive empathy (in terms of Theory of Mind) we also used the video-based Movie for the Assessment of Social Cognition (MASC, Dziobek et al., 2006). Not only did the test prove to have high interrater reliability and internal consistency and sensitivity, but the results also seem to be highly stable over time (Dziobek et al., 2006). The test involves watching a 15 min movie about four characters spending an evening together. It shows everyday social interactions, and is stopped 46 times for questions about the actors' feelings, thoughts, and intentions. Participants are required to choose the correct answer out of four possible ones. The test allows for a more differentiated analysis of specific patterns of social cognitive functioning with separate scores for the recognition of emotions, thoughts, and intentions. Sum scores for correct answers in all three sub-categories and a total score were computed. Moreover, the MASC also includes control questions that assess a participant's inferential processing concerning nonsocial stimulus material. The MASC has a good internal consistency with Cronbach's

Table 1
Socio-demographic and clinical variables of patients with narcissistic personality disorder (NPD), patients with borderline personality disorder (BPD), and healthy comparison subjects.

	Total NPD sample ($N=47$)		NPD without BPD ($N=22$)		Healthy subjects ($N=53$)		BPD without NPD ($N=27$)	
	M	S.D.	*M*	S.D.	*M*	S.D.	*M*	S.D.
Age (years)	32.4	8.0	34.4	8.3	33.2	10.7	30.0	8.3
Fluid intelligence[a]	115.2[1*]	12.0	114.9[2*]	10.6	120.9	10.87	114.7	11.0
Number of comorbid diagnosis	4.7	1.9	2.9	1.8			3.4	2.4
Previous suicide attempts	2.9	3.8	1.3[3***]	2.0			5.3	6.5
Previous hospitalizations (weeks)	22.4	39.4	8.6[3**]	12.9			42.4	61.1
GSI of SCL 90-R[c]	1.7[1***]	0.7	1.6[3*]	0.6	0.3	0.2	2.0	0.7
	N	%	*N*	%	*N*	%	*N*	%
Women	24[4]	51.0	8[5***]	36.4	29	54.7	25	92.6
Any affective disorder	33	70.2	16[5*]	72.7			10	37.0
MDE current	17	36.2	12[5*]	54.6			6	22.2
MDE lifetime	21	44.7	14[5*]	63.6			7	25.9
Dysthymia	16	34.0	5	22.7			4	14.8
Any substance use disorder	20	42.6	8	36.4			15	55.6
Any anxiety disorder	13	27.7	5	22.7			11	40.7
PTSD	7	14.9	1[4*]	4.6			8	29.6
Any eating disorder	10	21.3	4	18.2			8	29.6
Any cluster A PD	19	40.4	6	27.3			4	14.8
Any other cluster B PD[b]	26	55.3	4	18.2			8	29.6
Antisocial PD	12	25.5	4	18.2			4	14.8
Any cluster C PD	21	44.7	7	31.8			14	51.9
Without psychotropic medication	14	29.8	10	45.5			10	37.0
Antipsychotic	9	19.1	1	4.6			7	25.9
Antidepressant	26	55.3	11	50.0			17	63.0
Mood stabilizer	2	4.3	1	4.6			4	14.8

Note. NPD = narcissistic personality disorder, BPD = borderline personality disorder, MDE = major depression episode, PTSD = posttraumatic stress disorder, PD = personality disorder, [a]assessed with "Leistungs-Prüf-System" (LPS), [b]assessed with Symptom Checklist 90 Revised (SCL-90-R), [c]without NPD and BPD, [1]Mann–Whitney *U* test, [2]Kruskal–Wallis test, [3]ANOVA *F* test, [4]Fisher's exact test, [5]Pearson's χ^2, significance levels: $^*p<0.05$, $^{**}p<0.01$,$^{***}p<0.001$.

$\alpha=0.802$. The MASC sum score was significantly correlated with the MET score for cognitive empathy for healthy controls ($r=0.448$, $P=0.001$).

2.4. Statistical analysis

All statistical analyses were performed with SPSS version 15.0 (SPSS Inc., 2006). Before the use of parametric tests (for socio-demographic variables) to compare groups, Kolmogorov–Smirnov tests to assess normality and Levene's tests to assess homogeneity of variance were performed. Two-group comparisons (NPD vs. healthy controls) were performed with *t* tests; for all data without homogeneity of variances, Mann–Whitney *U* tests for two (NPD vs. healthy controls) and Kruskal–Wallis tests for three groups (NPD vs. BPD vs. healthy controls) were used, and for all categorical data (e.g., comorbid axis I and axis II disorders, gender), Pearson's χ^2 test or Fisher's exact test was calculated. Quantitative group mean measures (IRI, MET, and MASC) were compared using univariate and multivariate analyses of variance or covariance. To analyze between-group differences, general linear model estimated means were compared with a priori simple contrasts (to control for Type I errors). Gender was used as a covariate in all linear models when group differences were present. Convergence was established with Spearman's nonparametric coefficient to assess correlative associations between "lack of empathy" and IRI and MET measures (convergent validity). All analyses were two-tailed and the alpha level was set at $P<0.05$. Omega squares (ω^2) were used as measures of effect size ($\omega^2=0.010$ small, $\omega^2=0.059$ medium, $\omega^2=0.138$ large effect size; Kirk, 1996).

3. Results

3.1. Comparison between NPD and healthy controls

To assess cognitive and emotional empathy in NPD as measured with the IRI, a MANOVA model with perspective taking and empathic concern as dependent variables was conducted, which revealed a significant influence of group (Wilks' $\lambda=0.905$, $F_{2,95}=4.99$, $P=0.009$). Univariate between-subjects tests for IRI scales revealed significant differences in mean scores for cognitive empathy, but not for emotional empathy. Patients with NPD reported significantly lower scores on the IRI scale perspective taking (cognitive empathy) than healthy controls (Table 2).

To assess cognitive and emotional empathy with the MET task, a MANCOVA model with the test's subscales as dependent variables and background arousal as a covariate revealed a significant influence of group, (Wilks' $\lambda=0.764$, $F_{3,92}=9.48$, $P<0.001$). Univariate between-subjects tests displayed no significant differences of patients with NPD and healthy comparison subjects on cognitive empathy. Patients with NPD, however, showed significantly lower scores than healthy controls on the two emotional empathy scales (Table 2). To analyze cognitive empathy with the MASC, an ANOVA model with the MASC total score as the dependent variable revealed significantly lower scores for NPD patients than for controls, ($F_{1,95}=6.15$, $P=0.015$). MASC subscore analysis revealed no significant group effect (Wilks' $\lambda=0.947$, $F_{3,93}=1.748$, $P=0.163$). Follow up ANOVAs displayed a trend toward significance for all subscores, with lower values in the NPD group compared to healthy comparison subjects for the recognition of emotions, thoughts, and intentions (Table 2).

3.2. Comparison between NPD, BPD, and healthy controls

To test the specificity of impairments in empathy for NPD, only NPD patients without comorbid BPD were included in subsequent analyses and compared to a group of BPD patients without comorbid NPD and a group of healthy controls (for socio-demographic and clinical data see Table 1). Self-evaluation of empathy as measured by the IRI subscales (perspective taking and empathic concern) was included in a MANOVA as dependent variables, group (NPD, BPD, and healthy controls) as a fixed factor, and gender as a covariate. Analysis showed a significant influence of group (Wilks' $\lambda=0.902$, $F_{4,188}=2.50$, $P=0.044$). Comparison of a priori contrasts revealed significantly lower values for cognitive empathy in NPD and BPD patients compared to healthy subjects, whereas the emotional empathy scales only significantly differed between BPD and healthy controls (Table 3). To

Table 2
Means, standard deviations (S.D.), and group comparisons for subscales of IRI, MET, and MASC for patients with NPD and healthy comparison subjects.

Measure	Group				ANCOVA		
	NPD ($N=47$)		HC ($N=51$)				
	M	S.D.	*M*	S.D.	*F*	*P*	ω^2
IRI							
Cognitive empathy — *perspective taking*	21.32	4.39	23.84	3.59	9.726	0.002	0.082
Emotional empathy — *empathic concern*	24.80	4.33	26.04	3.18	2.626	0.108	0.016
MET[a]							
Cognitive empathy — *emotion recognition*	22.47	7.33	21.82	1.70	0.648	0.423	−0.002
Emotional empathy — *empathic concern*	4.68	1.57	5.80	1.40	25.405	<0.001	0.199
Emotional empathy — *mirroring emotions*	4.45	1.37	5.42	1.39	23.703	<0.001	0.188
MASC							
Cognitive empathy (total score)	30.77	4.94	33.34	5.26	6.150	0.015	0.049
Recognize emotions	10.38	2.35	11.10	2.15	2.474	0.119	0.015
Recognize thoughts	3.13	0.80	3.36	0.72	2.260	0.136	0.013
Recognize intentions	9.33	2.25	10.10	2.29	2.815	0.097	0.023

Note. NPD = narcissistic personality disorder, HC = healthy controls, IRI = Interpersonal Reactivity Index, MET = Multifaceted Empathy Test, MASC = Movie for the Assessment of Social Cognition, [a]The *F* tests the group effect. This test (ANCOVA) is based on the linearly independent pairwise comparisons among the estimated marginal means (covariate = background arousal). Degrees of Freedom: IRI and MASC: $d.f._{numerator}=1$, $d.f._{denominator}=95$; MET: $d.f._{numerator}=1$, $d.f._{denominator}=94$.

assess cognitive and emotional empathy with MET, a MANCOVA model with MET subscales as dependent variables (empathic concern, mirroring emotions, and emotion recognition) and background arousal and gender as covariates was conducted, and revealed a significant influence of group (Wilks' $\lambda=0.762$, $F_{6,182}=4.42$, $P<0.001$). In the a priori contrasts for the MET's cognitive empathy, patients with NPD displayed no significant differences compared to controls, but compared to BPD, contrasts revealed significantly higher cognitive empathy scores for patients with NPD ($P=0.022$, Table 3). By contrast, univariate between-subjects tests revealed significant differences between groups on the MET's emotional empathy scales but not on the cognitive empathy scale. For the a priori contrasts of the emotional empathy scales, patients with NPD showed significantly lower scores than controls on both emotional empathy scales (empathic concern, $P=0.014$, mirroring emotions, $P=0.019$). For a more detailed evaluation of cognitive empathy, an ANCOVA with the MASC's total score as the dependent variable and gender as a covariate revealed significant differences between groups ($F_{2,95}=3.53$, $P=0.033$), whereas contrasts solely revealed significant differences between patients with BPD and healthy controls ($P=0.011$), indicating unaffected cognitive empathy in NPD and deficits in BPD compared to healthy controls. MASC subscale analysis using a MANOVA displayed no significant group effect (Wilks' $\lambda=0.943$, $F_{6,186}=0.92$, $P=0.479$).

3.3. Convergent validity of "lack of empathy"

The DSM-IV criterion "lack of empathy" (measured as an ordinal variable by the SCID-II with: 1 = absent, 2 = subthreshold, and 3 = threshold) was negatively associated (Spearman's ρ) with the self-reported values for cognitive empathy (IRI; perspective taking: $\rho=-0.316$, $P=0.030$), but not with self-reported values for emotional empathy (IRI; empathic concern: $\rho=-0.026$, $P=0.400$). No correlative associations could be found for "lack of empathy" and cognitive or emotional empathy as measured by the MET (emotion recognition: $\rho=0.026$, $P=0.863$; empathic concern: $\rho=-0.142$, $P=0.341$; mirroring emotions: $\rho=-0.140$, $P=0.346$) or cognitive empathy as measured by the MASC (total score: $\rho=-0.159$, $P=0.286$).

Table 3
Means, standard deviations (S.D.), and group comparisons for subscales of IRI, MET, and MASC for patients with NPD, patients with BPD, and healthy controls.

	Group						ANCOVA			Simple contrasts (*P*)		
	1: NPD without BPD ($N=22$)		2: BPD without NPD ($N=27$)		3: HC ($N=53$)							
Measures	*M*	S.D.	*M*	S.D.	*M*	S.D.	*F*	*P*	ω^2	1 vs. 2	1 vs. 3	2 vs. 3
IRI[a]												
Cognitive empathy — *perspective taking*	21.73	4.13	21.21	4.86	23.86	3.63	4.095	0.020	0.058	0.820	0.041	0.017
Emotional empathy — *empathic concern*	25.15	3.70	24.38	6.99	25.98	3.18	2.058	0.133	0.021	0.181	0.746	0.046
MET[b]												
Cognitive empathy — *emotion recognition*	22.40	4.90	20.50	4.55	21.82	1.69	2.895	0.060	0.037	0.022	0.368	0.055
Emotional empathy — *empathic concern*	4.81	1.39	5.14	2.13	5.80	1.40	8.123	0.001	0.125	0.303	0.014	<0.001
Emotional empathy — *mirroring emotions*	4.55	1.26	4.70	1.80	5.42	1.39	10.71	<0.001	0.163	0.080	0.019	<0.001
MASC[a]												
Cognitive empathy (total score)	31.09	5.10	29.78	8.19	33.34	5.26	3.531	0.033	0.048	0.294	0.224	0.011
Recognize emotions	10.43	2.57	10.63	2.96	11.10	2.15	0.969	0.383	−0.001	0.626	0.485	0.184
Recognize thoughts	3.25	0.58	3.11	0.89	3.36	0.72	0.616	0.542	−0.008	0.933	0.423	0.350
Recognize intentions	9.56	2.37	8.85	2.55	10.10	2.28	2.520	0.086	0.029	0.258	0.437	0.028

Note. NPD = narcissistic personality disorder, BPD = borderline personality disorder, HC = healthy controls, IRI = Interpersonal Reaction Index, MET = Multifaceted Empathy Test, MASC = Movie for the Assessment of Social Cognition, [a]covariate = gender, [b]covariates = gender, background arousal. The *F* tests the group effects. These tests (ANCOVAs) are based on the linearly independent pairwise comparisons among the estimated marginal means (covariates = gender or gender and background arousal). Degrees of Freedom: IRI and MASC: $d.f._{numerator}=2$, $d.f._{denominator}=98$; MET: $d.f._{numerator}=2$, $d.f._{denominator}=97$.

4. Discussion

The NPD criterion "lack of empathy" has been listed in the DSM since 1980 although it has never been empirically established. In the current study we assessed emotional and cognitive empathy in a clinical sample of patients with a diagnosis of NPD. We used new ecologically valid instruments based on the multifaceted model of empathy. We could not confirm our a priori hypothesis; however, a different pattern of empathy impairment in NPD was found. Thus, the present data provide the first empirical evidence that NPD involves impaired emotional empathy, whereas cognitive empathy remains unaffected. Further, NPD patients overestimate their capacities for emotional empathy and show motivational deficits for cognitive empathy. A "near neighbor" comparison with BPD inpatients provided additional evidence that this pattern is characteristic of NPD. These findings challenge the way "lack of empathy" in NPD is currently conceptualized in the DSM-IV and illustrate that actual standardized assessment tools (e.g., the SCID-II interview) are insufficient for correctly capturing all aspects of "lack of empathy" in NPD.

4.1. Cognitive empathy

Assessing cognitive empathy via self-report (IRI) revealed significant impairment in patients with NPD. On the more objective and ecologically valid MET task, no deficit in cognitive empathy in the NPD patients could be detected. A closer look at the cognitive empathy items of the IRI reveals that they capture motivational aspects (all items include the phrasing "… I try to…"; Davis, 1980) rather than a capacity. Thus, underestimation of cognitive empathy on the IRI could reflect a motivational deficit; whereas unaffected performance on the cognitive empathy scale of the MET may capture normal capacity compared to controls.

Although the assessment of cognitive empathy by means of the sensitive MASC task revealed impairments in NPD patients, those impairments could not be replicated when comorbid BPD patients were excluded from the NPD sample. By contrast, but in accordance with prior research (Fonagy et al., 1996; Harari et al., 2010), BPD patients showed a trend toward impairment in cognitive empathy on the MET and clear deficits in cognitive empathy as measured by the MASC compared to controls, especially in recognizing the intentions of other persons. Thus, the subtle deficit in cognitive empathy as measured by the MASC sum score in the total NPD sample may be explained by BPD comorbidity. The finding of significantly better cognitive empathy measures in NPD patients compared to BPD patients on the MET, although not replicated with the MASC, also supports this argument. Further studies with a dimensional assessment of PD pathology should investigate the impact of subthreshold personality disorder pathology (e.g., BPD) on social cognition within NPD patients, in whom PD comorbidity is frequent (Westen et al., 2006).

4.2. Emotional empathy

NPD patients do not report impairments in emotional empathy as measured by the IRI. However, the more objective MET task clearly indicates impairments in emotional empathy in the NPD sample on both a mature (empathic concern) and more basic (mirroring emotions) level. Excluding patients with comorbid BPD from the NPD group, the emotional empathy impairment in NPD could be replicated. In the present study, both patient groups, NPD and BPD patients, displayed significantly impaired emotional empathy when compared to healthy controls. Our data suggest that patients with NPD are less able to mirror emotions and are less emotionally responsive to another person's emotional state compared to healthy controls. Interestingly, these deficits in emotional empathy are not perceived by NPD patients, as indicated by the unimpaired self-report IRI scales. Discrepancies in emotional empathy between the IRI and the MET/MASC may be related to an overestimation of competence in NPD patients. Subjects with narcissistic traits have been shown to overrate their task performance in social judgment and mind-reading skills, which was closely related to the typical narcissistic "self-aggrandizement" (Ames and Kammrath, 2004). In contrast to the more motivational IRI items on cognitive empathy, items for emotional empathy are more related to capacity/ability.

Thus, NPD patients show a characteristic pattern of empathy deficits compared to healthy controls, which includes overestimation of their capacity for emotional empathy with impairment in emotional empathy on a more ecologically valid task (MET). Further, they show preserved cognitive empathy ability with deficits in motivational aspects of cognitive empathy. Behavior specific to NPD could be ascribed to this characteristic pattern of an empathy deficit in NPD. As empathic concern or sympathy is often associated with prosocial behavior such as altruism (Decety and Hodges, 2006), a lack of emotional empathy could account for asocial behavior. Thus, arrogant, overtly disdainful, critical, or aggressive reactions toward others' feelings, or, in more severe forms, attempts to con, manipulate, or emotionally exploit others, could be due to an overestimation of emotional empathy with an actual lack of ability. Also, cognitive and emotional empathic functions have been found to be necessary for a person's relational competence, especially for maintaining romantic relationships (Davis and Oathout, 1987), which has been shown to be problematic for NPD patients. Also, in nonclinical samples of adults who show narcissism as a personality trait, lack of empathy has been linked to entitlement, exploitativeness (Watson et al., 1984), need for power, control, and dominance (Wiehe, 2003).

The present results suggest that NPD patients display a similar pattern of empathic deficits as has been described for psychopathic individuals in whom empathic dysfunction is also an essentially diagnostic criterion (Wiehe, 2003; Blair, 2005b; Goldberg et al., 2007). Psychopathy is associated with deficits in emotional empathy (Blair, 2005b; Goldberg et al., 2007) and largely unimpaired cognitive empathy (Richell et al., 2003; Dolan and Fullam, 2004). The neuroanatomical basis of psychopathy has been ascribed to a dysfunction of the amygdala (Kiehl et al., 2001), and one could speculate about a common amygdala dysfunction in psychopathy and NPD correlating to the deficit in emotional empathy.

With regard to BPD, our results argue for impaired emotional and cognitive empathy in these patients. The results of previous research on empathy in BPD had found impairment in cognitive empathy with preserved emotional empathy (Harari et al., 2010). In contrast to our study, BPD patients with comorbid axis I disorders were excluded in this study, which might explain discrepancies. Further research is needed to address this topic.

4.3. Convergent validity

Assessment of the NPD criterion "lack of empathy" is based on DSM description or SCID-II interview, both of which are not explicitly based on a theoretical construct of empathy. The DSM-IV diagnostic criterion "lack of empathy" is described as: "lacks empathy: is unwilling to recognize or identify with the feelings and needs of others." According to the wording "is unwilling," the criterion does not imply someone's *ability* to recognize or identify with the feelings and needs of others, but rather his/her *motivation*. Similarly, the exact wording in the SCID-II interview is as follows: "You've said that you're NOT really interested in other people's problems or feelings. (Tell me about that.)" And further: "You've said that people have complained to you that you don't listen to them or care about their feelings. (Tell me about that.)" (p. 27). Again, the wording does not assess the ability, but rather the motivation. IRI items of cognitive empathy also assess motivation (all items include the phrasing "…I try to…"; Davis, 1980) rather than ability. In our study, we found the self-report measure of cognitive empathy (IRI subscale "perspective taking") to

be negatively correlated with the criterion "lack of empathy" as measured by the SCID-II in NPD patients. This indicates that the SCID-II mainly assesses the subjectively perceived motivational deficit in cognitive empathy.

By contrast, the more objective and ecologically valid measure of emotional empathy by means of the MET did not correlate with the SCID-II parameter "lack of empathy," indicating that ability was not assessed by the SCID-II. To our knowledge, all previous studies that assessed sensitivity, specificity, and convergent validity of the criterion "lack of empathy," used DSM criteria or the SCID-II interview (Morey, 1985; Ronningstam and Gunderson, 1990; Blais et al., 1997; Holdwick et al., 1998; Gunderson and Ronningstam, 2001; Fossati et al., 2005). Thus, one conclusion of those data could be that the lack of convergent and divergent validity of the criterion "lack of empathy" in previous studies is mainly due to two points: First, the imprecise definition of empathy, focusing mainly on the motivational aspects and disregarding the multidimensional aspects of empathy, and second, the lack of appropriate assessment tools. Our data argue for a definition of "lack of empathy" based on an ability, at least in addition to motivation.

The study has some limitations. First, the presented results are based on a relatively small sample of psychiatric inpatients. Thus, our results have to be replicated in less impaired outpatient samples of patients with NPD. Also, further studies should take into account dimensional personality traits such as schizotypy (Henry et al., 2008) or psychopathy. Further studies should also address the topic of specificity of empathy impairment and behavioral consequences, for example, by including motor empathy (Blair, 2005a), using other complex social cognitive tasks (Golan et al., 2006; Zaki et al., 2008, 2009), or using in- and out-group designs (De Dreu et al., 2010). Also, the impact of state variables moderated by emotional regulation abilities (e.g. impact of anger, shame and envy) and self-esteem regulation abilities on empathic functioning should be addressed in future studies (see Tangney, 1995; Campbell et al., 2000; Netzlek et al., 2007).

The data provide the first empirical evidence that patients with NPD display significant impairments in emotional empathy, that is, the ability to feel what other people feel. In contrast, patients with NPD did not show deficits in cognitive empathy, that is, in taking another person's perspective. Furthermore, our data argue that subtle deficits in cognitive empathy in NPD patients are related to BPD comorbidity. Emotional empathy deficits seem to be shared with "near neighbor" BPD, whereas preliminary empirical evidence suggests that impairments in cognitive empathy abilities could to be more specific for BPD. In addition, NPD patients overestimate their abilities to show emotional empathy and report a motivational deficit for cognitive empathy compared to controls, whereas BPD patients don't. The current DSM-IV-based NPD symptom "lack of empathy" and the assessment by the SCID-II interview do not capture the deficits in emotional empathy measured in the present study with more ecologically valid tasks. We suggest a more precise theory based definition of the criterion "lack of empathy," and advocate for the use of more sensitive and multidimensional assessment tools for empathy in NPD.

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Manuskript A

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** beide Autoren haben in gleichen Teilen zum Manuskript beigetragen und teilen sich daher die Erstautorenschaft*

Do neuronal correlates of empathy differ in borderline personality disorder patients with and without posttraumatic stress disorder?

Isabel Dziobek,[1#] Sandra Preißler,[2,3#]* Isabela Heuser, [1,3]
Hauke R. Heekeren[1] & Stefan Roepke [1,3]

[1]Cluster of Excellence Languages of Emotion, Freie Universität Berlin,
Habelschwerdter Allee 45,
14195 Berlin, Germany
[2]Friedrich Schiller University Jena, Department of Biological and Clinical Psychology
Am Steiger 3, Haus 1,
07743 Jena
[3]Department of Psychiatry, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin,
Eschenallee 3,
14050 Berlin, Germany

[#]both authors contributed equally to this article

E-mail addresses:

Sandra Preißler	s.preissler@uni-jena.de
Isabel Dziobek	isabel.dziobek@fu-berlin.de
Hauke R. Heekeren	hauke.heekeren@fu-berlin.de
Stefan Roepke	stefan.roepke@charite.de

Correspondence should be addressed to:
Sandra Preißler
Friedrich Schiller University Jena, Department of Biological and Clinical Psychology
Am Steiger 3, Haus 1
07743 Jena

ABSTRACT

To explore the influence of posttraumatic stress disorder (PTSD) on neural correlates of empathy in patients with borderline personality disorder the sample of a former MRI study was halved in patients with PTSD and without. Independently of empathy results support a global model of hippocampal and orbitofrontal dysfunction in PTSD.

Keywords:

social cognition, hippocampus, orbitofrontal cortex

1 Introduction

Borderline personality disorder (BPD) is a severe psychiatric disorder characterized by a heterogeneous constellation of symptoms including interpersonal, behavioral, and emotional functioning (American Psychiatric Association, 2000). The heterogeneous clinical picture of BPD is influenced by its high rates of comorbidities (McGlashan et al., 2000; Zanarini et al., 1998; Zanarini, Frankenburg, Hennen, Reich, & Silk, 2004). Especially the rate of a co-occur post traumatic stress disorder (PTSD) in individuals with BPD is extremely high. Studies are reporting up to 58 % of BPD individuals also meeting PTSD criteria (Zanarini, et al., 2004). Both disorders share etiological factors, symptomatology and biological factors (Schmahl & Bremner, 2006).

Recently, the interpersonal impairments seen in BPD have been the focus of scientific study and debate (New, Goodman, Triebwasser, & Siever, 2008). Alterations in empathic functioning in BPD are a possible reason for these interpersonal deficits (Dziobek et al., 2011; Preißler, Dziobek, Ritter, Heekeren, & Roepke, 2010). There is clear evidence that empathy consists of at least two components (Decety & Meyer, 2008; Singer, 2006). The first one is a cognitive component. It describes the capacity to infer others' mental states and is also called mentalizing, Theory of Mind or social cognition (Blair, 2005). The second one is an affective component, which is the appropriate emotional reaction to another person (Davis, 1994).

It has been shown that patients with BPD have problems with both facets of empathy (Dziobek, et al., 2011; Preißler, et al., 2010) and that comorbid PTSD seems to worsen the empathic outcome at least in the cognitive component (Preißler, et al., 2010). Not only PTSD but also the level of intrusion, a symptom which commonly occurs in PTSD (American Psychiatric Association, 2000), and sexual abuse by a known assailant are shown to be negative predictors for cognitive empathic outcome (Preißler, et al., 2010).

In our recent study we could show specific neural correlates of cognitive and emotional empathy in patients with BPD (Dziobek, et al., 2011). Seen the high comorbidity with PTSD (Zanarini, et al., 2004) and the behavioral evidence, that PTSD worsen the empathic functioning of patients with BPD at least on a cognitive empathic level (Preißler, et al., 2010) we try to explore the influence of comorbid PTSD on the neural correlates of both facets of empathy in patients with BPD.

2 Methods

2.1 Participants

As described in our resent published study (cf. (Dziobek, et al., 2011) we included 30 women with BPD. In this sample 15 BPD patients suffered from comorbid PTSD (BPD_{PTSD}) and 15 did not (BPD_{noPTSD}). Both groups were matched in age (t_{28} = .067, p = .95) and IQ (t_{28} = .889, p = .38). All participants received a comprehensive diagnostically assessment (cf. (Dziobek, et al., 2011).
The ethics committee of the Charité- Universitätsmedizin Berlin approved the procedure, and participants provided written informed consent.

2.2 Multifaceted empathy test (MET) fMRI adaptation

Neuronal correlates of empathy were investigated using an fMRI adaptation of the MET (Dziobek, et al., 2011; Kirchner, Hatri, Heekeren, & Dziobek, 2010). The same series of pictures were presented for the cognitive and emotional empathy condition as well as for a high-level baseline control condition, in which participants were asked to make inferences about physical appearance (gender and age judgments).

2.3 Experimental procedure

Stimuli were presented in a mixed blocked/event-related design using customized experimental control software (Presentation, Neurobehavioral Systems Inc., Albany, CA, http://www.neurobs.com/). Each of the 24 blocks of 10 stimuli was preceded by an introductory question (cognitive empathy: “What is the person feeling?”; emotional empathy: “How much are you feeling for the person?”; and physical appearance inference: “How old is the person/Is this person female or male?”). Each picture was presented for 4.5 sec and a response pair was shown at the bottom of each picture. Stimuli were presented with jittered interstimulus intervals (minimum 1.25 sec, maximum 21.25 sec, mean 7.45 sec) optimized using OptSeq2 (OptSeq; www.surfer.nmr.mgh.harvard.edu).

2.4 fMRI und MRI data acquisition

A 1.5-T MRI scanner (Siemens Magnetom Sonata, Erlangen, Germany) with a standard head coil to acquire whole brain MRI data was used. Head movement was minimized using a vacuum pad. Axially oriented functional images (T2*-weighted volumes) were acquired (TE: 40 ms; TR: 2500 ms; flip angle: 90°; FOV: 256 mm; matrix: 64 x 64; voxel size: 4 x 4 x 4 mm; 26 slices). After acquisition of functional images, one sagittally oriented T1-weighted volumes (TE: 3.56 ms; TR: 12.24 ms; flip angle: 23°; matrix: 256 x 256; voxel size: 1 x 1 x 1 mm^3) were acquired for registration of the functional images.

2.5 fMRI data analyses

FMRI data were analyzed using a mixed effects approach within the framework of the general linear model as implemented in FSL (FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). For detailed description of further data processing please refer to (Dziobek, et al., 2011).

3. Results

3.1 Behavior

Behavioural data showed no significant group effect for cognitive (t_{28} = -.046, p = .96) or emotional empathy ratings (t_{28} = .010, p = .99) or reaction times (cognitive empathy: t_{28} = -.001, p > .99; emotional empathy: t_{28} = -.430, p = .67), suggesting that both groups showed similar engagement in the experimental design as required.

3.2 FMRI

3.2.1 Cognitive empathy

Contrasting brain activity in cognitive empathy between patients with BPD_{noPTSD} and BPD_{PTSD}, we found greater changes in the BOLD signal in two clusters in BPD_{noPTSD}. The first detected cluster was in the left hippocampus (MNI coordinates: -16, -32, -10; cluster size = 624; see figure1).
Second we found in the cognitive empathy condition greater changes in the BOLD signal in left OFC (MNI coordinates: -30, 36, -8) in BPD_{noPTSD} (cluster size = 1392; see figure 1).

Please insert **Figure 1** about here.

Figure 1.

In the cognitive empathy condition greater activity in patients without posttraumatic stress disorder (PTSD) (N = 15) than in patients with PTSD (N = 15) A) in the left orbitofrontal cortex (Montreal-Neurological-Institute coordinates: -30, 36, -8, *P* = .005) and B) in the left hippocampus (Montreal-Neurological-Institute coordinates: -16, -32, -10, *P* = .005) could be found. Highlighted areas (A, B, C) indicate regions where difference in blood oxygen level dependent (BOLD) signal between groups was significant.
Bar graphs show BOLD signal change in C) left orbitofrontal cortex and D) left hippocampus in both empathy conditions and in the higher level baseline condition for each group. Error bars represent standard error of the mean.

3.2.2. Emotional empathy

By contrasting the brain activity in emotional empathy between BPD_{noPTSD} and BPD_{PTSD}, again we found greater increases in the BOLD signal in the left hippocampus (MNI coordinates: -30, -22, -8; cluster size: 16). This cluster presents a sub-cluster of the region of interest detected in cognitive empathy. A second minimal cluster could be detected in the OFC (MNI coordinates: -30, -22, -8;

cluster size: 8). Also this cluster presents a sub-region of the before detected cluster. None other cluster could be detected.

4. Discussion

In this study we aimed to show specific neural correlates of impaired cognitive empathic functioning in BPD_{PTSD} and BPD_{noPTSD}. In the fMRI all patients did an empathy task assessing cognitive as well as emotional empathy and a physical appearance condition (Dziobek, et al., 2011).

In cognitive empathy comparing BPD_{PTSD} to BPD_{noPTSD} two clusters could be detected. One cluster was located in the left OFC and the other in the left hippocampus. In these regions of interest (ROIs) a detailed inspection of the BOLD response suggests that the activation difference between the groups is neither specific for cognitive empathy, nor for emotional empathy nor for physical appearance. In these ROIs the difference between BPD_{PTSD} and BPD_{noPTSD} seems to be given in all three conditions. As in all three conditions the same emotional pictures were presented, it may be a typical pattern of different activity for rather more basal emotion processing. BPD_{PTSD} compared to BPD_{noPTSD} show less activity independently of the instruction.

It has to be mentioned that in our previous study (Preißler, et al., 2010) comorbid PTSD was associated with impairment in cognitive empathy in BPD, especially for recognition of thoughts and intentions so a specific neural correlate for PTSD and cognitive empathy was expected. But the recognition of intentions and thoughts may be a more complex and no basic process of cognitive empathy. So we assume that the used MET (Dziobek, et al., 2011; Kirchner, Hatri, Heekeren, & Dziobek, 2011) potentially measures rather basal cognitive empathy (e.g. recognition of emotions) than higher order cognitive empathy processes (e.g. recognition of thoughts or intentions).

The function of the OFC can be seen in the context of conceptualisation (Kringelbach & Rolls, 2003). They describe the OFC as responsible for the ability of rapid change of behavior and fast decoding of face expressions. They propose that the OFC is crucial for controlling affective responses to salient stimuli. Mention this and in the light of the potential effects of fear conditioning in PTSD (Rauch, Shin, & Phelps, 2006) BPD_{PTSD} may recruit the OFC less than BPD_{noPTSD}. For both patient groups emotional faces may be permanent salient stimuli, but as consequence of actual stress reactions the BPD_{PTSD} failed to recruit this area as much as BPD_{noPTSD}. This found support in the results of Bremner and collaborators (Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Staib, et al., 2003). They found greater deactivation in OFC and in the left hippocampus in patients with PTSD when they recall emotional words (Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Staib, et al., 2003).

Similar as in (Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Staib, et al., 2003) not only the detected hyporesponsiveness of the OFC but also the result of the hippocampus goes in line with the neurocircuit model of PTSD described by (Rauch, et al., 2006). Beside a possible

hyperresponsibility of the amygdalae they hypothesize a deficiency in the ventromedial prefrontal cortex including the OFC and a hippocampal deficiency for patients with PTSD (Rauch, et al., 2006).

In contrast to the OFC is the hippocampus an area which is long discussed in BPD and PTSD as well. (For a circumstantiated discussion please refer to (Lewis & Grenyer, 2009)). Bremner and collaborators showed significantly decreased hippocampal blood flow during retrieval of memories of abuse in PTSD (Bremner et al., 1997; Bremner, Vythilingam, Vermetten, Southwick, McGlashan, Nazeer, et al., 2003). Although Shin and collaborators (Shin et al., 2002) found less recruitment of hippocampus in firefighters with PTSD, relative to firefighters without PTSD.

Together, our results also support the model of hippocampal and orbitofrontal dysfunction in PTSD, but to specify the influence of PTSD on neurocircuits of empathy an empathy task focusing on higher order empathic functioning seems to be needed.

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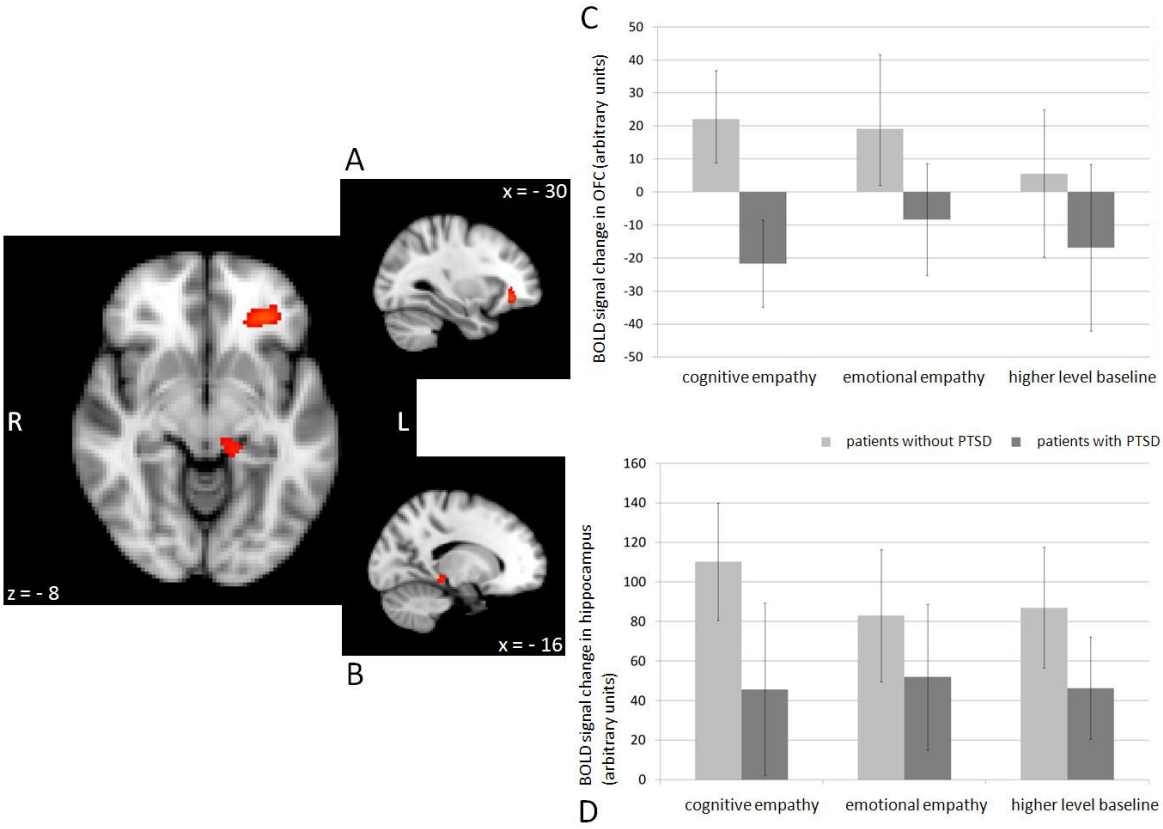
Figure 1.


A
x = - 30
R
L
z = - 8
x = - 16
B
C
BOLD signal change in OFC (arbitrary units)
50
40
30
20
10
0
-10
-20
-30
-40
-50
cognitive empathy
emotional empathy
higher level baseline
patients without PTSD
patients with PTSD
BOLD signal change in hippocampus (arbitrary units)
160
140
120
100
80
60
40
20
0
cognitive empathy
emotional empathy
higher level baseline
D

Supplemented table 1. Demographic characteristics, clinical characteristics and performance of patients with BPD with comorbid PTSD and patients with BPD without comorbid PTSD, respectively.

Measure	**patients with BPD without PTSD (n = 15)**		**patients with BPD with PTSD (n = 15)**			
	Mean	SD	Mean	SD	t value (df = 28)	p value
Age in years	26.93	9.10	26.73	7.13	.067	.95
Verbal IQ	98.54	9.46	95	10.37	.889	.38
IQ reasoning	121.64	10.64	118.86	12.38	.644	.53
BDI score	33.00	13.82	35.76	9.61	-.614	.54
BSL total score	2.35	0.92	2.29	0.56	.206	.84
Axis I comorbidity	No.	%	No.	%	X^2 value	p value
MDE Current	6	40	5	33.34	.144	.71
Lifetime	10	66.67	3	20	6.652	.01
Dysthymia	1	6.67	3	20	1.154	.28
Panic disorder	1	6.67	0	0	1.034	.31
Agoraphobia	4	26.67	1	6.67	2.160	.14
Posttraumatic stress disorder	0	0	15	100	30	.00
Social phobia	2	13.34	2	13.34	.000	1.00
Bulimia nervosa	4	26.67	3	20	.186	.67
Obsessive-compulsive disorder	0	0	3	20	3.333	.07
Axis II comorbidity	No.	%	No.	%	X^2 value	p value
Schizoid PD	0	0	0	0	-	-
Paranoid PD	0	0	0	0	-	-
Schizotypal PD	0	0	0	0	-	-
Histrionic PD	0	0	0	0	-	-
Narcissistic PD	1	6.67	0	0	1.034	.31
Antisocial PD	2	13.34	0	0	2.143	.14
Obsessive-compulsive PD	2	13.34	0	0	2.143	.14
Avoidant PD	4	26.67	4	26.67	.000	1.00

Dependent PD	0	0	1	6.67	1.034	.31

MET	Mean	SD	Mean	SD	t- value (df = 28)	p- value
cognitve empathy	.92	.18	.92	.11	-.046	.96
emotional empathy	1.47	.23	1.55	.22	.010	.99

reaction time in msec	Mean	SD	Mean	SD	t- value (df = 28)	p- value
cognitve empathy	2224.12	366.01	2224.27	225.05	-.001	1.00
emotional empathy	2117.91	370.72	2173.25	333.28	-.430	.67

Manuskript B

Bruehl, H., Preißler, S., Heuser, I., Heekeren, H. R., Roepke, S.*, Dziobek, I.* (2011). Increased prefrontal cortical thickness is associated with enhanced abilities to regulate emotions in PTSD-free women with borderline personality disorder.

** beide Autoren teilen sich die Letztautorenschaft*

Increased prefrontal cortical thickness is associated with enhanced abilities to regulate emotions in PTSD-free women with Borderline Personality Disorder

Hannah Bruehl[1]*, Sandra Preissler[2], Isabella Heuser[3,4], Hauke R. Heekeren[1,4], Stefan Roepke[3,4#] and Isabel Dziobek[4#]

[1] Department of Psychology of Emotion and Affective Neuroscience, Freie Universität Berlin
[2] Department of Biological und Clinical Psychology, University of Jena
[3] Charite-Universitätsmedizin Berlin, Department of Psychiatry and Psychotherapy
[4] Cluster Languages of Emotion, Freie Universität Berlin

[#]*shared last authorship*

**corresponding author*
Hannah Bruehl
Habelschwerdter Allee 45
Room JK 25/222h
14195 Berlin
hannah.bruehl@fu-berlin.de

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ABSTRACT

Background: Impaired frontolimbic circuitry has been implicated in the failure to adequately regulate emotions in Borderline Personality Disorder (BPD). Against this background, an anatomically based link is still missing. Furthermore, current results are convoluted by the high rate of comorbidity with Post Traumatic Stress Disorder (PTSD).

Methods: We evaluated 31 women with BPD (mean age 28 yrs), of which 17 had no comorbid PTSD (BPD-), and contrasted them to 29 age-matched control women on cortical thickness, amygdala volumes and neuropsychological variables including emotion regulation scores.

Results: The BPD women had increased cortical thickness in the dorsolateral PFC, which was driven by the BPD^- group. This increased thickness positively correlated specifically with emotion regulation scores in the BPD^- group only. Furthermore, in the BPD^- group, amygdala volume was positively associated with increased cortical thickness in the dorsolateral PFC.

Conclusions: Increased cortical thickness is present in the dorsolateral PFC of BPD^- and could reflect a compensatory neural mechanism for the affective impairment seen in BPD.

INTRODUCTION

Borderline Personality Disorder (BPD) is a severe psychiatric disorder, characterized by various abnormalities in interpersonal, behavioral and emotional functioning. Of these abnormalities, it has been postulated that the key feature of BPD is the inability to adequately regulate emotions (1). On the neural level, the ability to regulate emotions is assumed to be represented by a network of regions encompassing the hippocampus, amygdala and prefrontal cortex (PFC) (2).

The majority of neuroimaging studies with BPD patients have yielded structural and functional abnormalities in accordance with this suggested network. However, overall the findings are quite heterogeneous. Specifically, smaller hippocampal and, to some degree, smaller amygdalar volumes have been most consistently described in BPD (cf. 3; 4), although there are also accounts of no differences (5), or even larger volumes (6) in comparison to non-clinical controls. Furthermore, relative volumetric reductions and decreased grey matter density in various subregions of the PFC have been reported. For example, the orbitofrontal cortex, anterior cingulate cortex and dorsolateral PFC have been shown to be affected by BPD in some studies (7; 6; 8) however, not all (9; 10).

The structural neuroimaging studies in BPD did not link structural changes in the brain to emotion regulation abilities. However, functional neuroimaging studies have demonstrated abnormalities in response to emotional stimulus material. Those studies showed that the amygdala displays enhanced activation in BPD (11; 12) and this hyperactivity correlates with self-reported deficits in emotion regulation (13). In addition to the aberrant amygdala response, prefrontal hypometabolism (14; 15) and diminished recruitment of prefrontal regions when regulating emotional reactions have been observed in BPD patients (16). Taken together, these neuroimaging findings have stipulated the idea of a dysfunctional fronto-limbic network in BPD underlying emotional dysregulation (3). Yet, thus far, it has not been assessed whether there is a link between the structural brain abnormalities and impaired emotion regulation in BPD.

Moreover, both the impaired emotion regulation and brain abnormalities reported in BPD also occur in post-traumatic stress disorder (PTSD) patients. PTSD is comorbid with BPD in about 50% of cases (17; 18). Consequently, virtually all studies on BPD have included cases with PTSD. PTSD is associated with smaller hippocampal and amygdalar volumes (19) and there is also evidence for reduced PFC volume (20). In addition, abnormalities in amygdala-PFC activation have been reported (21). Thus, it remains unclear, which of the brain abnormalities observed in BPD are specific to the disorder itself or are a consequence of comorbid PTSD. In fact, based on the findings in PTSD, the same idea as formulated for BPD, of a hyperactive amygdala and defective inhibition from a hypoactive PFC has been suggested for PTSD, as well. In their recent paper, Schmahl et al. (22) compared BPD patients with and without PTSD to non-clinical controls on hippocampal and amygdalar volumes. They found that only those patients with co-morbid PTSD had smaller hippcampal volumes than non-clinical controls, thereby highlighting the importance of disentangling their respective effects on the brain.

Therefore, the primary aim of this study was to identify brain regions that are specific to BPD without the impact of comorbid PTSD. To this end, we compared patients with BPD with and without comorbid PTSD to non-clinical controls and among one another. Second, we wanted to scrutinize whether the brain regions thus identified would be related to emotional dysregulation in a group of currently unmedicated patients with BPD. Based on prior findings in the literature, we hypothesized, that we would find abnormalities in the PFC and amygdala. We chose cortical thickness, a new and innovative analysis method as our major means of assessing prefrontal brain integrity, given that it might be more sensitive to subtle changes than voxel-based morphometry, which involves confounding factors introduced by normalization (23). In addition, cortical thickness measurements have recently been validated as being similarly sensitive as manual tracing. For the amygdala, which cannot be assessed in terms of cortical thickness, we chose to follow a semiautomated volumetric approach, which has recently been shown to be a reliable measure for limbic structures (24).

METHODS

Participants

Thirty-one unmedicated women with a diagnosis of BPD and 27 non-clinical age-matched control women (NC) participated in the study. Fourteen of the patients with BPD also had a diagnosis for PTSD (BPD+), the other 17 did not (BPD-). Axis I and II diagnoses were made using the Mini–International Neuropsychiatric Interview (M.I.N.I.) (25) and the Structured Clinical Interview (SCID) for DSM-IV Axis II Disorders (26). All participants were free from psychotropic medication for at least two weeks before entering the study. A current neurological disorder, any current medical disorder that could affect cerebral metabolism, age below 18 years, and an IQ below 80 served as exclusion criteria. In addition patients with BPD were not included in the study if they had a current anorexia nervosa, psychotic disorder, or substance use disorder within the past six months.

The study was approved by the ethics committee of the Charité-University Medicine Berlin and all participants provided written informed consent.

Neuropsychological Assessment

All participants received a comprehensive neuropsychological assessment (cf. 27), including the Borderline Symptom List (BSL), IQ tests, assessment of alexithymia (Toronto Alexthymia Scale,TAS and the Bermond-Vorst Alexithymia Questionnaire, BVAQ) and a questionnaire for assessing the experience of emotions (Skalen zum Erleben von Emotionen, SEE). Briefly, the BSL is a dimensional self-report measure specifically developed to quantify borderline symptomatology (28). Crystalline intelligence was assessed by the verbal Wortschatztest (WST) and fluid intelligence by subtest 4 of the Leistungsprüfsystem 29 (30), which assesses reasoning skills. Both the TAS (31) and the BVAQ (32) are self report measures of alexithymia and yield a total score, where higher scores indicate larger proneness to alexithymia. The ability to regulate emotions was assessed using the SEE questionnaire (33). The SEE is an established German questionnaire, which consists of seven independent

subscales. For the purpose of this study, the subscale assessing emotion regulation was used, where higher scores indicate better abilities to regulate emotions.

Magnetic Resonance Imaging

Images were acquired on a 1.5-T MRI scanner (Siemens Magnetom Sonata, Erlangen, Germany) with a standard head coil for whole brain MRI data. Two sagittally oriented T1-weighted volume (TE: 3.56 ms; TR: 12.24 ms; flip angle: 23°; matrix: 256 x 256; voxel size: 1 x 1 x 1 mm) were acquired and used for further processing by the freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The freesurfer tool allows quantitative assessment of structural brain data without rater bias.

a) Cortical Thickness Measurements

Cortical thickness measurements, which are described in detail in Fischl and Dale (34) were obtained by reconstructing representations of the gray/white matter boundary (35) and the cortical surface and then calculating the distance between those surfaces at each vertex across the cortical mantle. This method uses both intensity and continuity information from the entire 3-dimensional magnetic resonance volume in segmentation and deformation procedures to construct representations of cortical thickness. The maps produced are not restricted to the voxel resolution of the original data and thus, are capable of detecting submillimeter differences between groups (34). This has been validated using histology and magnetic resonance (36; 37). Thickness measures may be mapped on the inflated surface of each participant's reconstructed brain. Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a standard deviation of 10 mm and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns. This procedure provides accurate matching of morphologically homologous cortical locations among participants, resulting in a mean measure of cortical thickness for each group at each point on the reconstructed surface. The entire cortex in each participant

was visually inspected, and any inaccuracies in segmentation were manually corrected by persons with extensive training in brain anatomy who were blind to group membership.

Statistical comparisons of global data and surface maps were generated by computing a general linear model of the effects of each variable (group membership, demographic and neuropsychological variables) on thickness at each vertex.

Cortical thickness clusters were first displayed using a threshold that shows all vertices with *p*-values between 0.03 and 0.01. To avoid type I error inflation, Monte Carlo simulation was then conducted to correct for multiple comparisons on the significant clusters, using a vertex-wise threshold of $p< 0.05$. The Monte Carlo simulation creates multiple null datasets, from which a distribution of cluster sizes is derived. From that, the cluster size corresponding to the desired corrected *p*-value can be read off. From the thus generated cluster, we created an ROI on the group average brain that was mapped back to each individual subject using spherical morphing to find homologous regions across subjects and yield a mean thickness score over the location for each subject.

To validate primary associations between cortical thickness and neuropsychological test scores we took advantage of the built-in function of the freesurfer software, to feed in behavioral variables into the general linear model. This approach constitutes an unbiased way to look for associations between behavioral variables and cortical thickness across the entire cortex.

b) Voxel based morphometry (VBM)

To validate our cortical thickness measurements and allow comparison to other neuroimaging studies with BPD patients, we furthermore applied VBM to our data, using fsl VBM (38; 39) carried out with fsl tools (40). First, structural images were brain-extracted using BET (41). Next, tissue-type segmentation was carried out using FAST4 (42). The resulting grey-matter partial volume images were then aligned to MNI152 standard space using the affine registration tool FLIRT (43; 44), followed optionally by nonlinear registration using FNIRT, which uses a b-spline representation of the registration warp field (45). The

resulting images were averaged to create a study-specific template, to which the native grey matter images were then non-linearly re-registered. The registered partial volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. The modulated segmentated images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Finally, voxelwise general linear model was applied using permutation-based non-parametric testing (5000 permutations), correcting for multiple comparisons across space. Voxel-based thresholding, both uncorrected and corrected, for multiple comparisons was adopted. The significance level with the familywise error (FWE) corrected was set at $p< 0.05$.

b) Semiautomated amygdala segmentation

Segmentation of subcortical deep gray matter volumetric structures, including the amygdala, was carried out using the freesurfer tool and has been described in detail by Fischl et al. (46; 47). The volumes so derived were used for the purpose of establishing associations to cortical thickness data.

Statistical Analysis

Demographic variables and the comparison of neuropsychological variables between NC and all BPD as well as segmentation imaging data were compared using two-tailed independent samples t-tests. Neuropsychological variables between the NC and BPD+ and BPD-, respectively, and between the BPD+ and BPD- groups were compared using univariate ANOVAs with Tukey post-hoc tests. Statistical analysis of cortical thickness and VBM data was carried out using the general linear model (see detailed explanation above). Fisher's Z was used to compare correlations. All analyses were carried out using the freesurfer and fsl tool, respectively and PASW Statistics software package (version 18.0, SPSS Inc., an IBM Company, Chicago, IL, USA).

RESULTS

Demographics and Neuropsychology

Patients with BPD were comparable to NC with respect to age. As expected, they differed significantly on the BSL, TAS, BVAQ and emotion regulation abilities (SEE). In addition, they also differed significantly on IQ and BMI. When comparing BPD^- patients to NC, the IQ and BMI differences present in the larger group disappeared, whereas the differences on the BSL, TAS, BVAQ and SEE remained the same. Comparing BPD^+ patients to NC showed the same differences, as well as a trend for differences on IQ and BMI. None of the assessed scores were significantly different between the BPD^+ and BPD^- group. Please refer to table 1 for an overview of the group means.

Insert table 1 about here

Cortical Thickness

After correcting for multiple comparisons, the general linear model comparing NC to all BPD indicated increased regional cortical thickness in the BPD group in a circumscribed cluster (Cluster 1) located in the right rostralmiddlefrontal cortex (mean cortical thickness NC: 2.83±0.16 mm vs. BPD: 3.09±0.21 mm). The cluster had a size of 861 mm^2 and MNI305 coordinates of the maximum were *18.4 56.3 -14.7*. No significant differences were detected for the left hemisphere. Please refer to figure 1A for a display of the cluster.

Since our primary goal was to identify brain changes specific to BPD without comorbid PTSD, we then restricted the analysis of cortical thickness to BPD^- patients. After correction for multiple comparisons, we found increased regional cortical thickness in the right hemisphere, which was essentially identical to what was found when comparing NC to all BPD. Specifically, cortical thickening was detected in a confined cluster of 856 mm^2 (Cluster 2), located within the right rostralmiddlefrontal cortex (mean cortical thickness NC: 2.73±0.17 mm vs. BPD^-: 3.01±0.25 mm, MNI305 coordinates of the maximum: *18.8 56.8 -14.3*). Please refer to figure 1B for a display of Cluster 2. No significant differences in cortical thickness

were detected in the left hemisphere, or for either hemisphere when comparing NC to BPD^+ and BPD^- with BPD^+.

VBM

For ease of comparison to other structural studies on BPD, we then conducted an independent analysis using VBM. Paralleling our cortical thickness results, we found increased grey matter density in the right prefrontal cortex, amongst others, when comparing BPD and BPD^- to NC *(p= 0.01 uncorrected,* see figure 2*)*. However, this finding did not survive FWE correction.

Amygdala Volume

Descriptively, amygdala volume was reduced in the BPD^- compared to NC (right amygdala BPD^-: 1.60±0.12 cc vs. NC: 1.66±0.19 cc; left amygdala BPD^-: 1.48±0.13 cc vs. NC: 1.52±0.18 cc), however, this difference was not statistically significant.

Brain-Behavior Relationships

Since we had found regional cortical thickening in the BPD^- group, in the next step we tested whether there were any associations between the ability to regulate emotions and cortical thickness in NC and BPD^-. We found a significant correlation in the BPD^- group between the cluster that had separated the NC and BPD^- group (Cluster 2) and the SEE emotion regulation score (r= 0.682, *p*= 0.003). Whereas in BPD^- an increase in regional cortical thickness corresponded to better abilities to regulate emotions in the right hemisphere, this relationship was not present in NC (r= 0.035, *p*= 0.864 Fisher's z= 2.37, *p*= 0.018, see figure 1C). To validate this finding, we then further took advantage of the built-in function of the freesurfer software, to feed in behavioral variables into the general linear model, thus allowing for an independent analysis at the whole brain level. After correcting for multiple comparisons, we found that in a cluster (Cluster 3) located within the right rostralmiddlefrontal cortex, largely overlapping with Cluster 2 (cluster size: 873 mm^2; mean

cortical thickness NC: 2.55±0.15 mm vs. BPD^-: 2.73±0.31 mm; MNI305 coordinates of the maximum: *39.2 48.8 -2.7*), the relationship between the ability to regulate emotions and cortical thickness was significantly different in NC and BPD^- (NC: r= 0.095 , BPD^-: r= 0.765, Fisher's z= -2.69, *p*= 0.007), confirming our initial results. No other clusters were detected and considering other neuropsychological variables (BSL, TAS, BVAQ) did not yield any results. Please refer to figure 1D for the display of Cluster 3.

Brain-Brain Relationships

Because the amygdala has been implicated in emotional dysregulation in BPD (12) and a functional prefrontal-amygdala disconnection has been described in BPD (5), we additionally investigated the relationship between regional cortical thickening and amygdala volume in an exploratory way in the group of BPD^-. We found a significant positive correlation between cortical thickness in the cluster that had been associated with emotion regulation based on whole brain analyses (Cluster 3) and right amygdala volume in BPD^- (r= 0.553, *p*= 0.021), whereas this association was negative, albeit only at trend level, in the control group (r= -0.364, *p*= 0.067).

INSERT FIGURES 1A-D ABOUT HERE

INSERT FIGURE 2 ABOUT HERE

DISCUSSION

The primary aim of this study was to identify brain alterations that are specific to Borderline Personality Disorder (BPD) without accompanying Posttraumatic-Stress-Disorder (PTSD). To this end, we used a direct measurement of cortical thickness in order to be able to catch subtle differences between groups.

Our results provide first evidence for increased cortical thickness in the right rostralmiddlefrontal cortex, which is part of the dorsolateral PFC (dlPFC), among a group of unmedicated patients with BPD, where this finding was specific to those patients without PTSD (BPD^-). Furthermore, we show that the increased cortical thickness in the dlPFC of BPD^- is associated with enhanced emotion regulation abilities, commensurate with the assumed role of the dlPFC in emotion regulation. Lastly, our findings also provide support for an anatomical basis of an altered frontolimbic circuit in the context of emotion regulation in PTSD-free BPD patients, since amygdala volume in BPD^- was related to cortical thickeness in the dlPFC.

To the best of our knowledge, this is the first account of cortical thickness in BPD patients. Borderline patients without an additional diagnosis of PTSD exhibited increased thickness in a confined area located in the right dlPFC. This alteration was not observed in patients with an additional diagnosis of PTSD. The dlPFC has been identified to be part of a distributed set of prefrontal regions that together orchestrate the regulation of emotion, presumably by keeping the response in limbic areas, such as the amygdala, at bay (48-51). This frontolimbic circuit is assumed to be disturbed in BPD, as hyperactivity of the amygdala (11; 12) and abnormal PFC functioning (5; 52; 16; 53; 54) in the context of the processing of emotion and affect have been reported.

Our present results situate themselves conceptually within this framework. By showing that in a group of BPD^- patients increased cortical thickness in the dlPFC is present, we demonstrate that there is an anatomical analog to the fMRT findings in BPD. So far, the dlPFC has been assessed in adults with BPD both manually and by using VBM, with no differences to non clinical controls being reported (9; 7; 10). The discrepancy of our to those

findings likely stems from both employing cortical thickness analysis rather than manual or semi automated techniques, as well as disentangling the impact of BPD and additional PTSD. Cortical thickness has been shown to be more sensitive to subtle differences than VBM, which involves confounding factors introduced by normalization (23). In addition, in the ROI-based studies, differences may have been present but remained undetected due to the size of the ROI, since here, we describe alterations manifesting in a small part of the dlPFC.

We found that the increased cortical thickness in the dlPFC was related to better emotion regulation abilities. Of note, this relationship was confirmed by an independent whole brain analysis, strengthening our finding. This is in agreement with a recent structural study, which showed an inverse association between dlPFC volume and impulsiveness in BPD patients (55). However, since the association between dlPFC and emotion regulation was only present in our group of BPD^- patients, it could be interpreted as reflecting an anatomical basis for a compensatory mechanism with respect to emotion regulation, which comes into play only in those BPD patients that do not have an additional PTSD diagnosis.

Although it is not uncommon to find increased cortical thickness in a disease group i.e., (56), how increased cortical thickness develops and how this suggested compensation might be operant in BPD would need to be ascertained in future studies, ideally with a longitudinal design. Reduced grey matter density in the dlPFC of teenagers with BPD suggests that the PFC is affected early on in the course of the disease (8). Thus it is conceivable that those patients that do not develop additional PTSD, might ultimately present with a more favorable cerebral phenotype, including focally increased cortical thickness, than those that do receive an additional diagnosis. Although we cannot draw conclusions as to the causal relationship between the neuroanatomical finding and affective impairment, the association found here strengthens the argument that BPD is largely conceptualized as a disorder of impaired emotion regulation (1; 57) and that this impairment is reflected on the neuroanatomical level, as well.

We did not detect overt differences with respect to cortical thickness between BPD^- and BPD^+. This negative finding between the non-PTSD and PTSD group is somewhat at odds with the current neuroimaging literature on PTSD (58). However, it has to be noted that the majority of the PTSD literature is mostly concerned with combat veterans, and using different imaging analysis methods. In women with abuse-related PTSD, which more closely resembles our current sample, no cortical thickness differences have been detected between PTSD patients and controls (59), corroborating our current findings. The differences observed in our sample between BPD^- but not BPD^+ and non clinical control group may thus become apparent only in the context of emotion regulation.

Interpreting the right-hemispheric lateralization is not straightforward, because little prior work speaks directly to this issue in the context of BPD or emotion regulation. Driessen and coworkers have shown differentially lateralized activation of the PFC in BPD^+ and BPD^- during the processing of traumatic events (60). They postulated different neuronal networks within BPD depending on the presence or absence of PTSD.

Lastly, in addition to the relationship between cortical thickness and emotion regulation, we also found that the volume of the right amygdala was descriptively reduced in the BPD^- group and this volume was positively associated with cortical thickness in the dlPFC. Reduced amygdala volume in BPD in the absence of PTSD has been reported (61). There are plenty of bidirectional projections between the amygdala and PFC (62) and emotion regulation has been associated with the relationship between the two structures (63). Speculatively, the positive relationship between amygdala volume and cortical thickness in the dlPFC could reflect the anatomical correlate of an altered frontolimbic circuit in BPD in the context of emotion regulation. However, it has to be noted that amygdala volume and emotion regulation were not directly associated with one another in our sample, limiting the conclusions that can be drawn from this result.

Our study has several strengths. First, in comparison to other studies, we had a relatively big sample size. Second, in our main analyses, we excluded those patients with PTSD, which can be considered a significant confound in other studies on BPD. Third, our patients were not taking any medication at the time of study. Lastly, we chose cortical thickness analysis as our main means of assessing the brain, which is considered a sensitive method, geared at detecting even subtle changes of the brain. With that being said, our study has several limitations. The use of semiautomated volumetric assessment of the amygdala can be considered suboptimal because of the gross overestimation of volumes in comparison to manual tracing. However, our point was not to assess absolute volumes of the amygdala in BPD, but to establish correlations to the PFC, which should be relatively unaffected by this bias. Furthermore, our study design does not permit us to draw conclusions about cause and effect of the relationship between emotional dysregulation and brain alterations. Future studies could address this issue by employing a longitudinal design with therapy aimed at improving emotion regulation capabilities. Another potential concern of our study is the assessment of emotion regulation. A more comprehensive assessment would be informative about which subprocesses of emotion regulation are specifically associated with alterations in the PFC. Lastly, a combination of structural, including DTI, and functional neuroimaging would be desirable to establish a link between the structural alterations we find in BPD and online processes of emotion regulation in BPD.

In conclusion, we demonstrated increased cortical thickness in a confined area in the right dlPFC in unmedicated and PTSD-free patients with BPD. This increased cortical thickness was related to emotion regulation and amygdala volumes, possibly reflecting a compensatory neural mechanism for affective impairments in BPD.

ACKNOWLEDGEMENTS

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Table 1. Descriptives of non-clinical controls (NC), patients with BPD, patients with BPD without comorbid PTSD (BPD^-) and BPD patients with PTSD (BPD^+), respectively.

	NC (N = 27)	BPD (N = 31)	BPD^- (N = 17)	BPD^+ (N = 14)
Measure	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
age (in years)	28.22 ± 8.22	26.71 ± 7.88	26.82 ± 8.70	26.57 ± 7.07
BMI (m^2/kg)*	22.53 ± 4.00	25.65 ± 6.82	24.5 ± 6.32	26.97 ± 7.37
BSL**, #, ##	68.08 ± 54.73	215.42 ± 70.50	215.47 ± 82.74	215.36 ± 55.18
TAS**, #, ##	37.87 ± 8.43	61.11 ± 11.39	59.07 ± 13.49	63.67 ± 7.87
BVAQ**, #, ##	12.22 ± 1.87	15.23 ± 2.44	15.12 ± 2.17	15.37 ± 2.83
IQ (LPS subtest 4)	122.70 ± 11.42	118.90 ± 12.06	119.88 ± 11.17	117.79 ± 13.35
IQ (WST)*	102.48 ± 9.15	96.10 ± 9.67	97.73 ± 9.10	94.36 ± 10.32
Emo reg (SEE) **, #, ##	13.19 ± 2.66	9.23 ± 2.21	9.53 ± 2.15	8.85 ± 2.30

*** NC vs BPD p< 0.001*

**NC vs BPD p<0.05*

#NC vs BPD^- p<0.05

##NC vs BPD^+ p<0.05

Abbreviations: PTSD, posttraumatic stress disorder; SD, standard deviation; BMI, body mass index; BSL, Borderline Symptom List; TAS, Toronto Alexithymia Scale; BVAQ, Bermond-Vorst Alexithymia Questionnaire; IQ, intelligence quotient; LPS, Leistungsprüfsystem; WST, Wortschatztest; SEE, Skalen zum Erleben von Emotionen.

Figure Legends.

Figure 1.

A: Increased cortical thickness (blue clusters) in the right rostralmiddlefrontal cortex in the BPD vs. NC group -Cluster 1,

B: The BPD^- vs. NC group -Cluster 2,

C: Increased cortical thickness is associated with better abilities to regulate emotions in BPD^-

D: The association with emotion regulation-Cluster 3. Clusters shown are clusters that survived correction for multiple comparisons with corrected *p*= 0.05.

Figure 2. Results of the VBM analysis. Upper half: increased grey matter density in the PFC of all BPD compared to NC (cluster size: 32 voxels, *MNI coordinates: 36 60 -14*). Lower half: increased grey matter density in the PFC of BPD^- compared to NC (cluster size: 20 voxels, MNI coordinates: *38 58 -14*). Clusters shown at *p*= 0.01 uncorrected.

Figures.

Figure 1A.

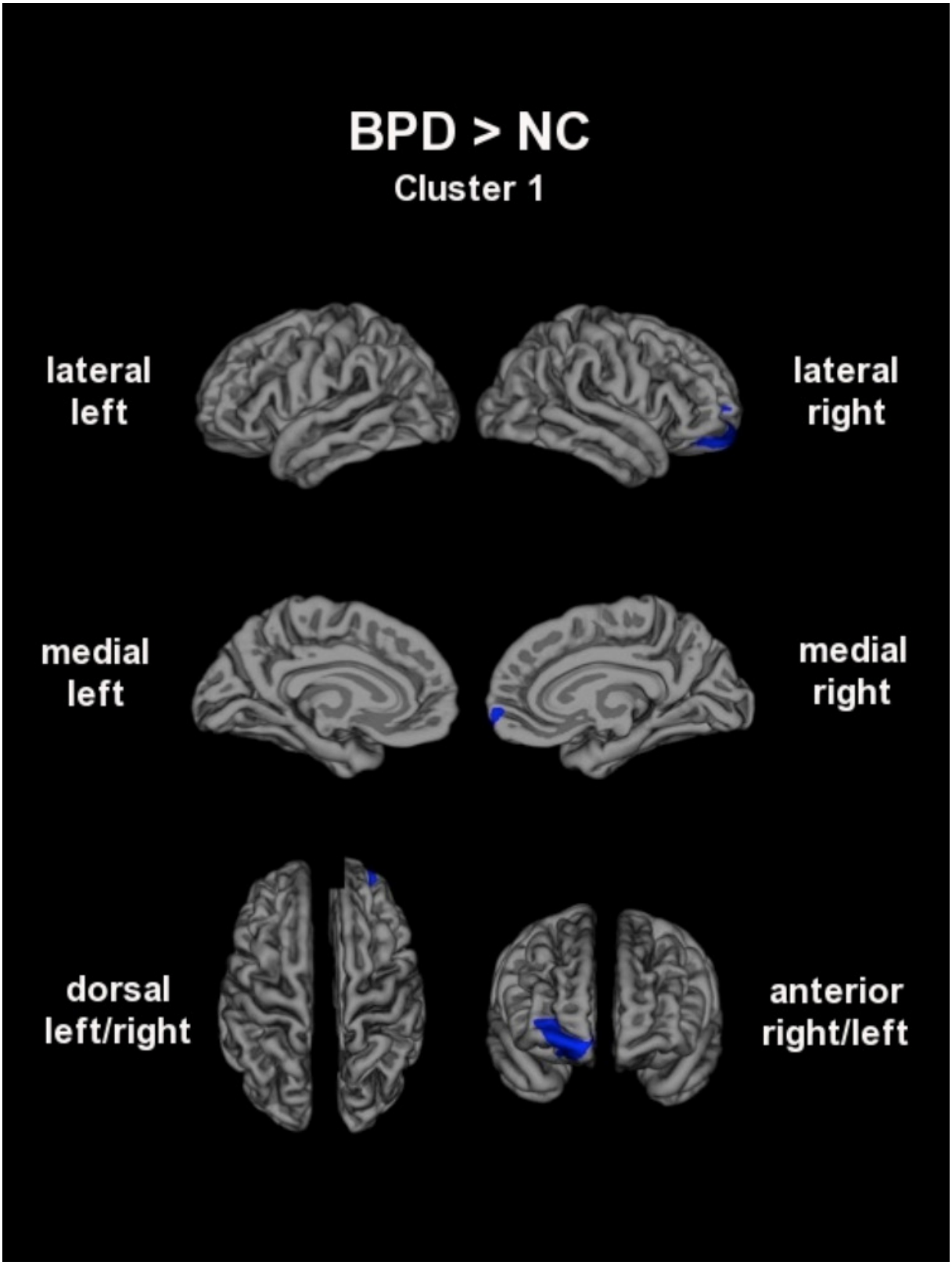


Figure 1B.

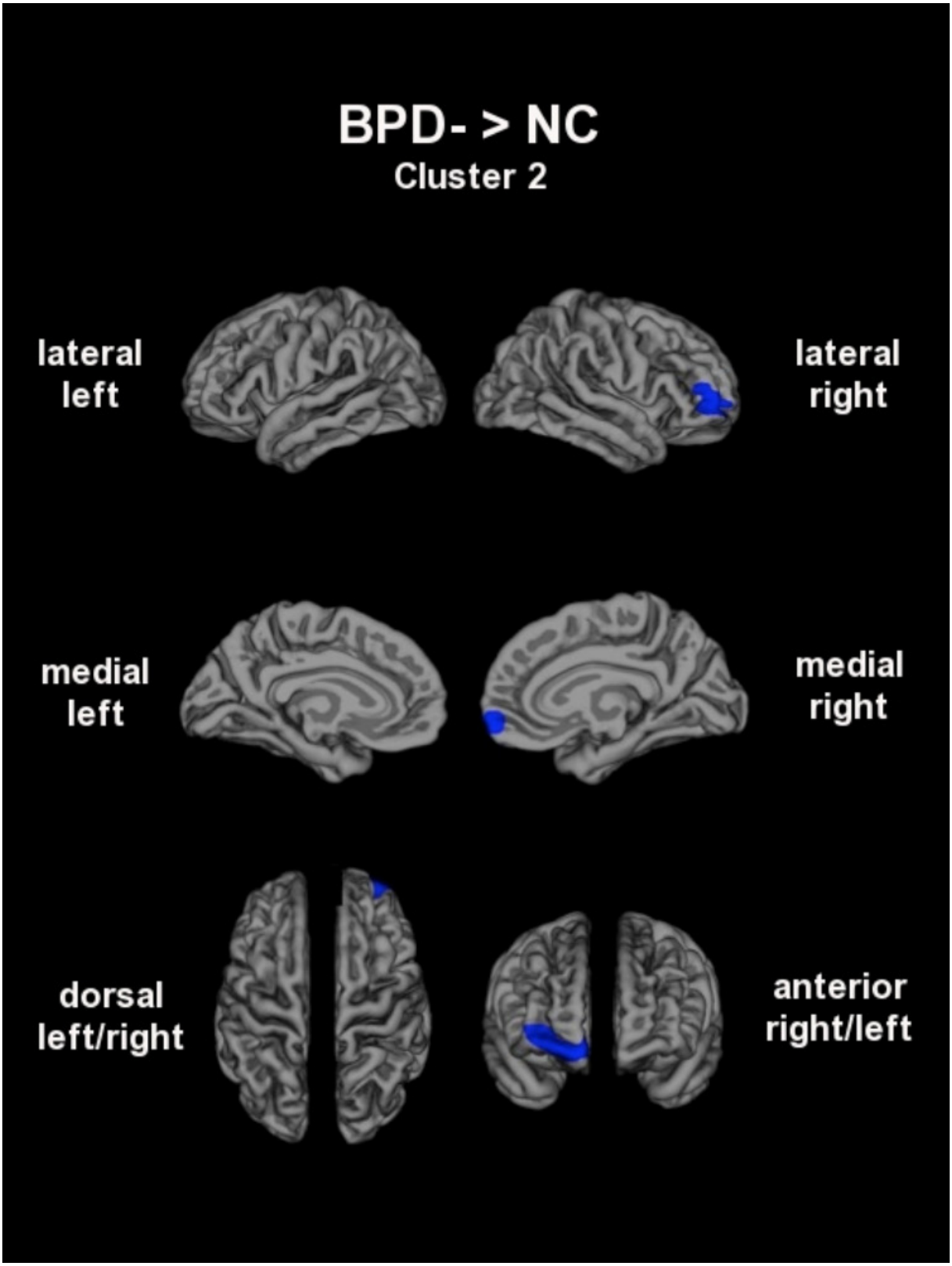

BPD- > NC
Cluster 2
lateral left
lateral right
medial left
medial right
dorsal left/right
anterior right/left

Figure 1C.

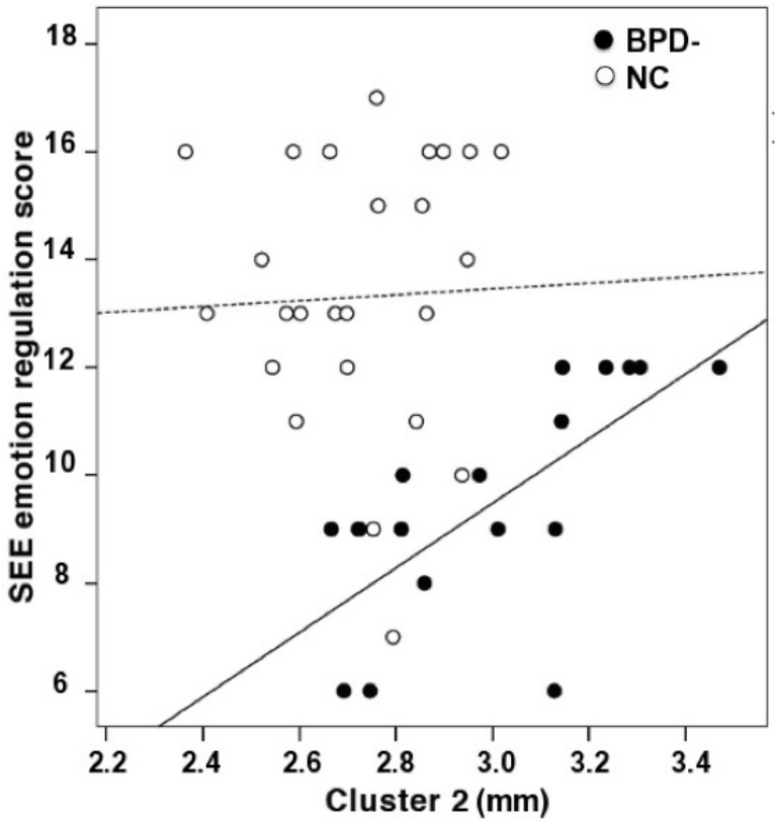

BPD-
NC
SEE emotion regulation score
18
16
14
12
10
8
6
2.2
2.4
2.6
2.8
3.0
3.2
3.4
Cluster 2 (mm)

Figure 1D.

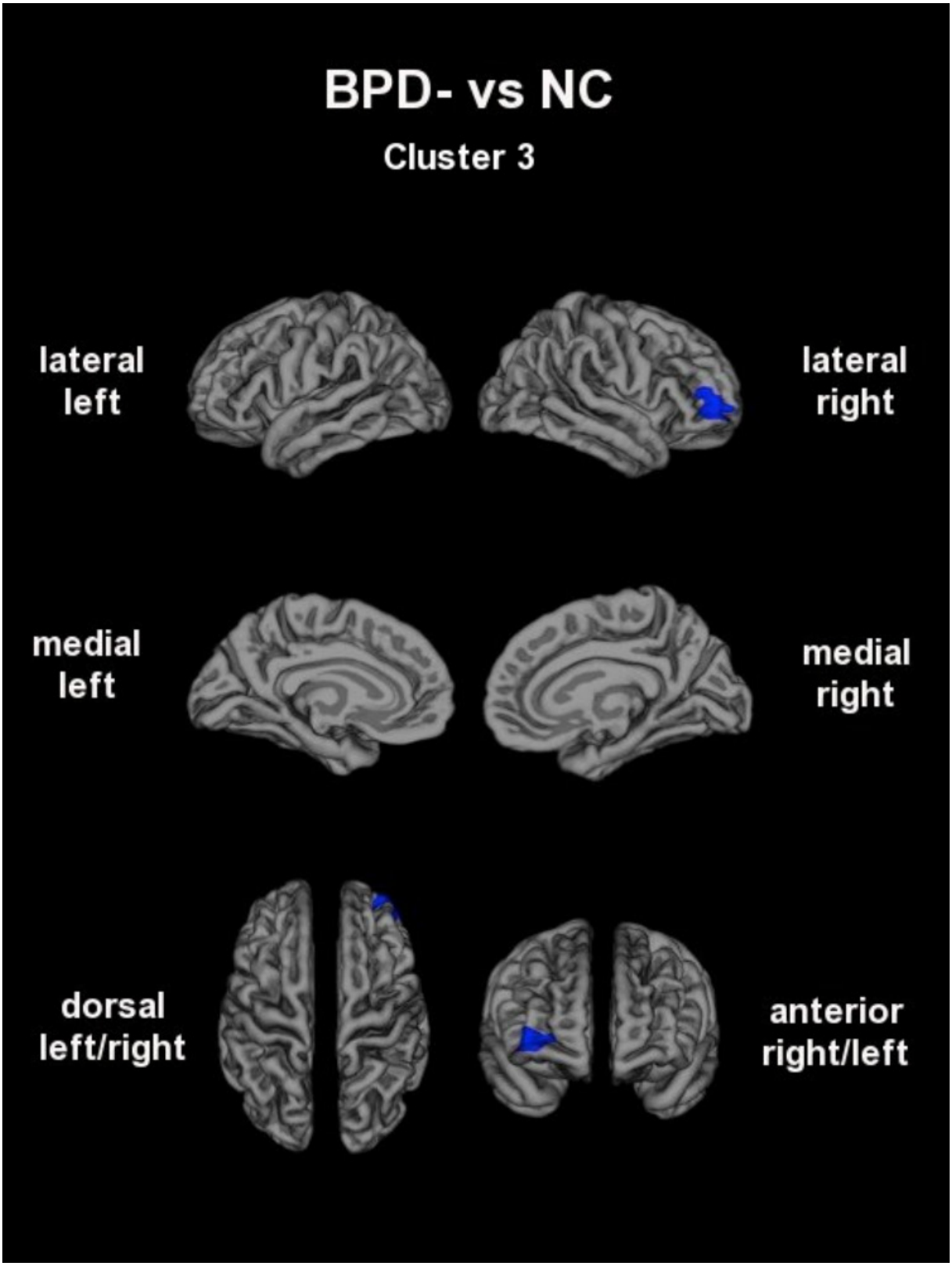
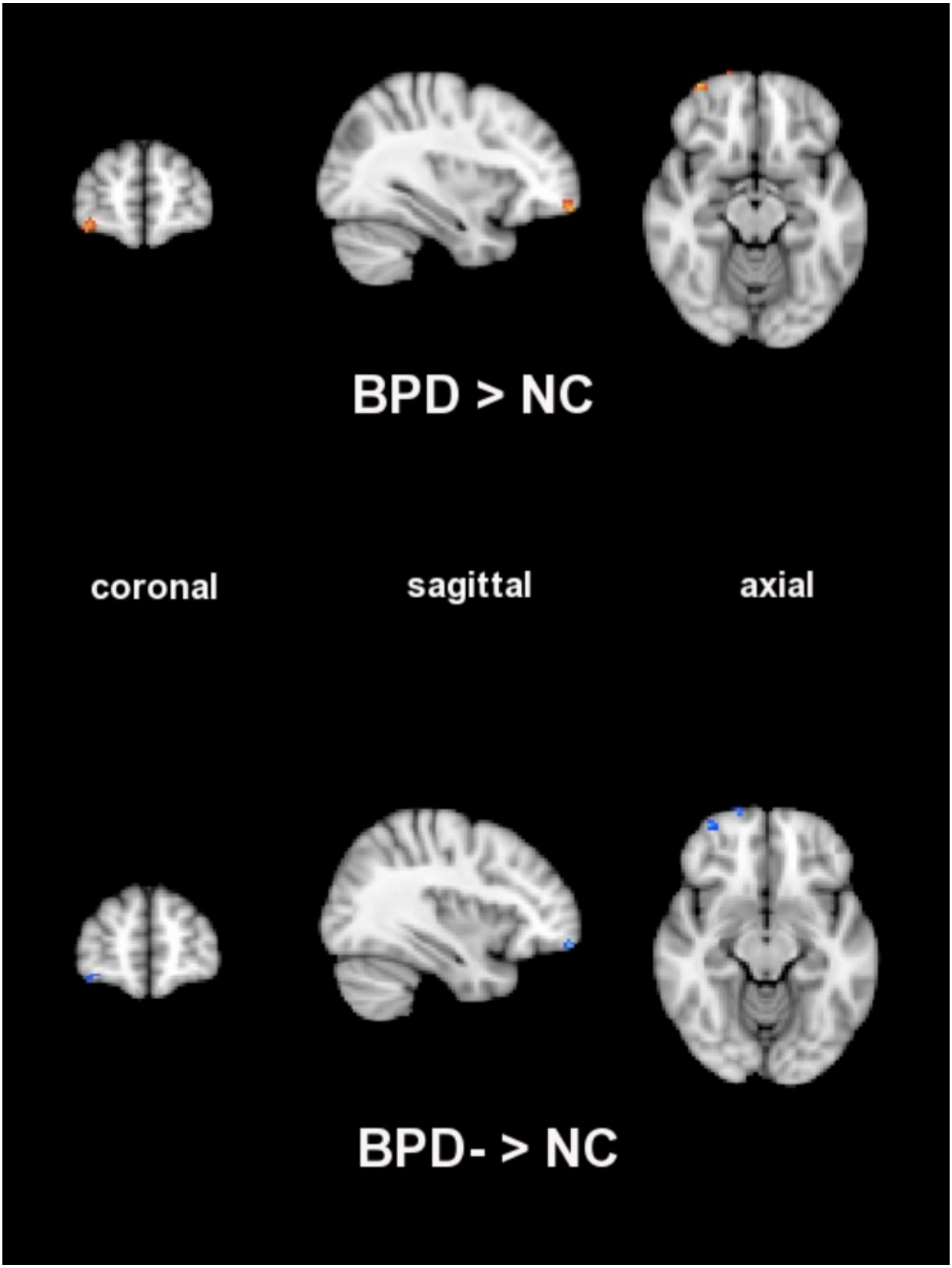

BPD- vs NC
Cluster 3
lateral left
lateral right
medial left
medial right
dorsal left/right
anterior right/left

Figure 2.



Eidesstattliche Erklärung

Hiermit erkläre ich, dass mir die Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät II, der Humboldt-Universität zu Berlin vom 17.01.2005, zuletzt geändert am 13.02.2006, veröffentlicht im Amtlichen Mitteilungsblatt Nr. 34/2006 bekannt ist. Ich erkläre außerdem, dass ich die Dissertation selbst angefertigt und alle von mir benutzten Hilfsmittel, persönliche Mitteilungen und Quellen in meiner Arbeit angegeben sind. Außerdem erkläre ich, dass meine Erklärung zum Eigenanteil an den eingereichten Manuskripten und Publikationen vollständig ist und dass ich darüber hinaus keine Hilfe bei der Auswahl und Auswertung des Materials sowie bei der Erstellung der Dissertation in Anspruch genommen habe. Dritte haben weder mittelbar noch unmittelbar geldwerte Leistungen von mir für Arbeiten erhalten, die in Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen. Die Dissertation wurde noch nicht als Prüfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung eingereicht. Zudem wurde keine gleiche, keine in wesentlichen Teilen ähnliche und auch keine andere Abhandlung bei einer anderen Hochschule beziehungsweise anderen Fakultät als Dissertation eingereicht. Zuletzt versichere ich, dass ich noch keinen Doktorgrad im Fach Psychologie besitze.

Jena, den 18. Juni 2012

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Sandra Preißler